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☐	L1	(protein tyrosine kinase adj3 2 or Pyk adj3 2) and crystal	36

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☐ 1. Document ID: US 6987000 B2

L1: Entry 1 of 36 File: USPT Jan 17, 2006

US-PAT-NO: 6987000
DOCUMENT-IDENTIFIER: US 6987000 B2

TITLE: Cark protein and nucleic acid molecules and uses therefor

DATE-ISSUED: January 17, 2006

PRIOR-PUBLICATION:

DOC-ID	DATE
US 20040110232 A1	June 10, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Raju; Jeyaseelan	Acton	MA		US

US-CL-CURRENT: 435/15; 435/194, 435/252.3, 435/320.1, 435/325, 530/350

ABSTRACT:

The invention provides isolated nucleic acids molecules, designated CARK nucleic acid molecules. The invention also provides antisense nucleic acid molecules, recombinant expression vectors containing CARK nucleic acid molecules, host cells into which the expression vectors have been introduced, and nonhuman transgenic animals in which a CARK gene has been introduced or disrupted. The invention still further provides isolated CARK proteins, fusion proteins, antigenic peptides and anti-CARK antibodies. Diagnostic methods utilizing compositions of the invention are also provided.

8 Claims, 35 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 35

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 2. Document ID: US 6921763 B2

L1: Entry 2 of 36 File: USPT Jul 26, 2005

US-PAT-NO: 6921763

DOCUMENT-IDENTIFIER: US 6921763 B2

TITLE: Pyrazolopyrimidines as therapeutic agents

DATE-ISSUED: July 26, 2005

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hirst; Gavin C.	Marlborough	MA		
Rafferty; Paul	Westborough	MA		
Ritter; Kurt	Newton	MA		
Calderwood; David	Framingham	MA		
Wishart; Neil	Jefferson	MA		
Arnold; Lee D.	Westborough	MA		
Friedman; Michael M.	Newton	MA		

US-CL-CURRENT: 514/262.1; 544/262

ABSTRACT:

The present invention is directed to pyrazolopyrimidine derivatives of formula (I)
##STR1##

wherein the substituents are defined herein, which are useful as kinase inhibitors and as such are useful for affecting angiogenesis and diseases and conditions associated with angiogenesis.

132 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 3. Document ID: US 6894051 B1

L1: Entry 3 of 36 File: USPT May 17, 2005

US-PAT-NO: 6894051
DOCUMENT-IDENTIFIER: US 6894051 B1

TITLE: Crystal modification of a N-phenyl-2-pyrimidineamine derivative, processes for its manufacture and its use

DATE-ISSUED: May 17, 2005

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Zimmermann; Jurg	Basel			CH
Sutter; Bertrand	Hesingue			FR
Burger; Hans Michael	Allschwil			CH

US-CL-CURRENT: 514/252.18; 544/295

ABSTRACT:

The invention relates to a new crystalline form of the methanesulfonic acid addition salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl) pyrimidin-2 -ylamino)phenyl]benzamide of formula 1, which may be used for example for tumor therapy.

18 Claims, 3 Drawing figures
Exemplary Claim Number: 1,15
Number of Drawing Sheets: 2

☐ 4. Document ID: US 6881401 B1

L1: Entry 4 of 36 File: USPT Apr 19, 2005

US-PAT-NO: 6881401
DOCUMENT-IDENTIFIER: US 6881401 B1

TITLE: Methods of treatment of immune system related disorders using Neutrokine-alpha

DATE-ISSUED: April 19, 2005

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Yu; Guo-Liang	Berkeley	CA		
Ebner; Reinhard	Gaithersburg	MD		
Ni; Jian	Rockville	MD		
Rosen; Craig A.	Laytonsville	MD		

US-CL-CURRENT: 424/85.1; 424/185.1, 424/198.1, 514/12, 514/2, 530/350, 530/351, 530/399

ABSTRACT:

The present invention relates to a novel Neutrokine-alpha, and a splice variant thereof designated Neutrokine-alphaSV, polynucleotides and polypeptides which are members of the TNF family. In particular, isolated nucleic acid molecules are provided encoding the human Neutrokine-alpha and/or Neutrokine-alphaSV polypeptides, including soluble forms of the extracellular domain. Neutrokine-alpha and/or Neutrokine-alphaSV polypeptides are also provided as are vectors, host cells and recombinant methods for producing the same. The invention further relates to screening methods for identifying agonists and antagonists of Neutrokine-alpha and/or Neutrokine-alphaSV activity. Also provided are diagnostic methods for detecting immune system-related disorders and therapeutic methods for treating immune system-related disorders.

98 Claims, 34 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 22

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D.

☐ 5. Document ID: US 6828320 B2

L1: Entry 5 of 36 File: USPT Dec 7, 2004

US-PAT-NO: 6828320
DOCUMENT-IDENTIFIER: US 6828320 B2

TITLE: Heterocyclic compounds

DATE-ISSUED: December 7, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Cockerill; George Stuart	Bedford			GB
Carter; Malcolm Clive	Ware			GB
Guntrip; Stephen Barry	Hertford			GB
Smith; Kathryn Jane	Bishop's Stortford			GB

US-CL-CURRENT: 514/233.5; 514/312

ABSTRACT:

Substituted heteroaromatic compounds, and in particular substituted quinolines and quinazolines, are protein tyrosine kinase inhibitors. The compounds are described as are methods for their preparation, pharmaceutical compositions including such compounds and their use in medicine, for example in the treatment of cancer and psoriasis.

23 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D.

☐ 6. Document ID: US 6812327 B1

L1: Entry 6 of 36 File: USPT Nov 2, 2004

US-PAT-NO: 6812327
DOCUMENT-IDENTIFIER: US 6812327 B1
**** See image for Certificate of Correction ****

TITLE: Neutrokine-alpha polypeptides

DATE-ISSUED: November 2, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY

Yu; Guo-Liang	Berkeley	CA
Ebner; Reinhard	Gaithersburg	MD
Ni; Jian	Rockville	MD
Rosen; Craig A.	Laytonsville	MD

US-CL-CURRENT: 530/351; 424/198.1, 424/85.1, 435/69.5, 530/300, 530/350, 530/399

ABSTRACT:

The present invention relates to a novel Neutrokine-alpha, and a splice variant thereof designated Neutrokine-alphaSV, polynucleotides and polypeptides which are members of the TNF family. In particular isolated nucleic acid molecules are provided encoding the human Neutrokine-alpha and/or Neutrokine-alphaSV polypeptides, including soluble forms of the extracellular domain. Neutrokine-alpha and/or Neutrokine-alphaSV agonists and antagonists of Neutrokine-alpha and/or Neutrokine-alphaSV activity. Also producing the same. The invention further relates to screening methods for identifying agonists and antagonists of Neutrokine-alpha and/or Neutrokine-alphaSV activity. Also provided are diagnostic methods for detecting immune system-related disorders and therapeutic methods for treating immune system-related disorders.

223 Claims, 34 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 22

☐ 7. Document ID: US 6797513 B2

L1: Entry 7 of 36 File: USPT Sep 28, 2004

US-PAT-NO: 6797513
DOCUMENT-IDENTIFIER: US 6797513 B2

TITLE: Nucleic acid encoding CLK2 protein kinases

DATE-ISSUED: September 28, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Ullrich; Axel	Munchen			DE
Nayler; Oliver	Graefehing			DE

US-CL-CURRENT: 435/325; 435/194, 435/252.3, 435/254.11, 435/320.1, 435/69.1, 530/300, 530/350, 536/23.1, 536/23.5

ABSTRACT:

The present invention relates to nucleic acid molecules encoding mCLK2, mCLK3, and mCLK4 polypeptides, nucleic acid molecules-encoding portions of their amino acid sequences, nucleic acid vectors harboring such nucleic acid molecules, cells containing such nucleic acid vectors, purified polypeptides encoded by such nucleic

acid molecules, and antibodies to such polypeptides. Also included are assays that contain at least one CLK protein kinase related molecule. Diagnosis and treatment of an abnormal condition related to RNA splicing or cell proliferation in an organism by using a CLK protein kinase related molecule or compound are disclosed. A method of using a CLK protein kinase related molecule or compound as a contraceptive to reproduction in male organisms is also disclosed.

8 Claims, 7 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 7

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 8. Document ID: US 6797501 B2

L1: Entry 8 of 36 File: USPT Sep 28, 2004

US-PAT-NO: 6797501
DOCUMENT-IDENTIFIER: US 6797501 B2

TITLE: Protein tyrosine phosphatase PTP20 and related products and methods

DATE-ISSUED: September 28, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Aoki; Naohita	Nagoya			JP
Ullrich; Axel	Martinsried			DE

US-CL-CURRENT: 435/194; 435/195, 435/196, 435/252.3, 435/320.1, 530/300, 530/350, 536/23.2

ABSTRACT:

The present invention relates to a novel polypeptide, PTP20, and to nucleic acid molecules encoding the polypeptide. The invention also relates to nucleic acid molecules encoding portions of the phosphatase, nucleic acid vectors containing PTP20 related nucleic acid molecules, recombinant cells containing such nucleic acid vectors, polypeptides purified from such recombinant cells, antibodies to such polypeptides, and methods of identifying compounds that bind PTP20 or abrogate its interactions with natural binding partners. Also disclosed are methods for diagnosing abnormal conditions in an organism with PTP20 related molecules or compounds.

17 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 9. Document ID: US 6727256 B1

L1: Entry 9 of 36 File: USPT Apr 27, 2004

US-PAT-NO: 6727256
DOCUMENT-IDENTIFIER: US 6727256 B1

TITLE: Bicyclic heteroaromatic compounds as protein tyrosine kinase inhibitors

DATE-ISSUED: April 27, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Carter; Malcolm Clive	Ware			GB
Cockerill; George Stuart	Bedford			GB
Guntrip; Stephen Barry	Hertford			GB
Lackey; Karen Elizabeth	Hillsborough	NC		
Smith; Kathryn Jane	Bishop's Stortford			GB

US-CL-CURRENT: 514/266.1; 544/279, 544/283, 544/284, 544/293

ABSTRACT:

Substituted heteroaromatic compounds of formula (I), wherein X is N or CH; Y is CR.sup.1 and V is N; or Y is N and V is CR.sup.1 ; or Y is CR.sup.1 and V is CR.sup.2 ; or Y is CR.sup.2 and V is CR.sup.1 ; R.sup.1 represents a group CH.sub.3 SO.sub.2 CH.sub.2 CH.sub.2 NHCH.sub.2 --Ar--, wherein Ar is selected from phenyl, furan, thiophene, pyrrole and thiazole, each of which may optionally be substituted by one or two halo, C.sub.1-4 alkyl or C.sub.1-4 alkoxy groups; R.sup.2 is selected from the group comprising hydrogen, halo, hydroxy, C.sub.1-4 alkyl, C.sub.1-4 alkoxy, C.sub.1-4 alkylamino and di[C.sub.1-4 alkyl]amino; U represents a phenyl, pyridyl, 3H-imidazolyl, indolyl, isoindolyl, indolinyl, isoindolinyl, 1H-indazolyl, 2,3-dihydro-1H-indazolyl, 1H-benzimidazolyl, 2,3-dihydro-1H-benzimidazolyl or 1H-benzotriazolyl group, substituted by an R.sup.3 group and optionally substituted by at least one independently selected R.sup.4 group; R.sup.3 is selected from a group comprising benzyl, halo-, dihalo- and trihalobenzyl, benzoyl, pyridylmethyl, pyridylmethoxy, phenoxy, benzyloxy, halo-, dihalo- and trihalobenzyloxy and benzenesulphonyl, or R.sup.3 represents trihalomethylbenzyl or trihalomethylbenzyloxy; or R.sup.3 represents a group of formula (a) wherein each R.sup.5 is independently selected from halogen, C.sub.1-4 alkyl, C.sub.1-4 alkoxy; and n is 0 to 3; each R.sup.4 is independently hydroxy, halogen, C.sub.1-4 alkyl, C.sub.2-4 alkenyl, C.sub.2-4 alkynyl, C.sub.1-4 alkoxy, amino, C.sub.1-4 alkylamino, di[C.sub.1-4 alkyl]amino, C.sub.1-4 alkylthio, C.sub.1-4 alkylsulphinyl, C.sub.1-4 alkylsulphonyl, C.sub.1-4 alkylcarbonyl, carboxy, carbamoyl, C.sub.1-4 alkoxycarbonyl, C.sub.1-4 alkanoylamino, N-(C.sub.1-4 alkyl) carbamoyl, N,N-di(C.sub.1-4 alkyl)carbamoyl, cyano, nitro and trifluoromethyl; and salts and solvates thereof, are disclosed, as are methods for their preparation, pharmaceutical compositions containing them and their use in medicine.

8 Claims, 0 Drawing figures
Exemplary Claim Number: 1

☐ 10. Document ID: US 6723726 B1

L1: Entry 10 of 36 File: USPT Apr 20, 2004

US-PAT-NO: 6723726
DOCUMENT-IDENTIFIER: US 6723726 B1

TITLE: Protein tyrosine kinase inhibitors

DATE-ISSUED: April 20, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Cockerill; George Stuart	Bedford			GB
Carter; Malcolm Clive	Ware			GB
Guntrip; Stephen Barry	Hertford			GB
Smith; Kathryn Jane	Bishop's Stortford			GB

US-CL-CURRENT: 514/259.41; 514/252.02, 514/255.05, 544/238, 544/278

ABSTRACT:

Substituted heteroaromatic compounds, and in particular substituted bicyclic heteroaromatic compounds of formula (I), wherein X is N or CH; A represents a fused 5, 6 or 7-membered heterocyclic ring containing 1 to 5 heteroatoms which may be the same or different and which are selected from N, O or S(O).sub.m, wherein m is as defined above, the heterocyclic ring containing a total of 1, 2 or 3 double bonds inclusive of the bond in the pyridine or pyrimidine ring to which it is fused, with the provisos that the heterocyclic ring does not form part of a purine and that the fused heterocyclic ring does not contain two adjacent O or S(O).sub.m atoms. U represents a 5 to 10-membered mono or bicyclic ring system in which one or more of the carbon atoms is optionally replaced by a heteroatom independently selected from N, O and S(O).sub.m, wherein m is 0,1 or 2 and wherein the ring system is substituted by at least one independently selected R.sup.6 group and is optionally substituted by at least one independently selected R.sup.4 group, with the proviso that U does not represent phenyl; are protein tyrosine kinase inhibitors. The compounds are described as are methods for their preparation, pharmaceutical compositions including such compounds and their use in medicine, for example in the treatment of cancer and psoriasis.

15 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 11. Document ID: US 6713485 B2

L1: Entry 11 of 36 File: USPT Mar 30, 2004

US-PAT-NO: 6713485
DOCUMENT-IDENTIFIER: US 6713485 B2
** See image for Certificate of Correction **

TITLE: Heterocyclic compounds

DATE-ISSUED: March 30, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Carter; Malcolm Clive	Ware			GB
Cockerill; George Stuart	Bedford			GB
Guntrip; Stephen Barry	Hertford			GB
Lackey; Karen Elizabeth	Hillsborough	NC		
Smith; Kathryn Jane	Hertfordshire			GB

US-CL-CURRENT: 514/266.24; 544/293

ABSTRACT:

The present invention relates to substituted heteroaromatic compounds, methods for their preparation, pharmaceutical compositions containing them and their use in medicine. Specifically, the invention relates to quinazoline derivatives useful in treating disorders mediated by protein tyrosine kinase activity, in particular erbB-2 and/or EGFR activity.

18 Claims, 0 Drawing figures
Exemplary Claim Number: 1

☐ 12. Document ID: US 6706709 B2

L1: Entry 12 of 36 File: USPT Mar 16, 2004

US-PAT-NO: 6706709
DOCUMENT-IDENTIFIER: US 6706709 B2

TITLE: Indolinone derivatives as protein kinase/phosphatase inhibitors

DATE-ISSUED: March 16, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Tang; Peng Cho	Moraga	CA		
Harris; G. Davis	San Francisco	CA		
Li; Xiaoyuan	Los Altos	CA		

US-CL-CURRENT: 514/235.2; 544/143, 544/144, 548/455

ABSTRACT:

The present invention relates to certain 2-indolinone compounds which modulate the activity of protein kinases ("PKs") and phosphatases. The compounds of this invention are therefore useful in treating disorders related to abnormal PK

activity. Pharmaceutical compositions comprising these compounds, methods of treating diseases utilizing pharmaceutical compositions comprising these compounds and methods of preparing them are also disclosed.

8 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. D

☐ 13. Document ID: US 6689806 B1

L1: Entry 13 of 36 File: USPT Feb 10, 2004

US-PAT-NO: 6689806
DOCUMENT-IDENTIFIER: US 6689806 B1

TITLE: Indolinone compounds as kinase inhibitors

DATE-ISSUED: February 10, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Tang; Peng Cho	Moraga	CA		
Sun; Li	Foster City	CA		
McMahon; Gerald	San Francisco	CA		
Miller; Todd Anthony	Bend	OR		
Shirazian; Shahrzad	Corte Madera	CA		
Wei; Chung Chen	Foster City	CA		
Harris, Jr.; G. Davis	San Francisco	CA		
Li; Xiaoyuan	Los Altos	CA		
Liang; Congxin	Sunnyvale	CA		

US-CL-CURRENT: 514/418; 514/414, 514/415, 548/465, 548/466, 548/468, 548/486

ABSTRACT:

The invention relates to certain indolinone compounds, their method of synthesis, and a combinatorial library consisting of the indolinone compounds of the invention. The invention also relates to methods of modulating the function of protein kinases using indolinone compounds of the invention and methods of treating diseases by modulating the function of protein kinases and related signal transduction pathways.

19 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. D

☐ 14. Document ID: US 6670348 B1

L1: Entry 14 of 36 File: USPT Dec 30, 2003

US-PAT-NO: 6670348
DOCUMENT-IDENTIFIER: US 6670348 B1
** See image for Certificate of Correction **

TITLE: Methods and compositions for destruction of selected proteins

DATE-ISSUED: December 30, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Rosen; Neal	Englewood	NJ		
Danishefsky; Samuel	Englewood	NY		
Ouerfelli; Ouathek	New York	NY		
Kuduk; Scott D.	Harleysville	PA		
Sepp-Lorenzino; Laura	New Haven	CT		

US-CL-CURRENT: 514/176; 514/182, 514/183, 514/26, 514/27, 514/450, 536/6.4, 540/107, 540/109, 540/112, 540/113, 540/115 , 540/2, 540/461, 549/268, 552/502, 552/625, 552/638

ABSTRACT:

Compounds having an ansamycin anitibiotic, or other moiety which binds to hsp90, coupled to a targeting moiety which binds specifically to a protein, receptor or marker can provide effective targeted delivery of the ansamycin antibiotic leading to the degradation of proteins and death of the targeted cells. These compositions may have different specificity than the ansamycin alone, allowing for a more specific targeting of the therapy, and can be effective in instances where the ansamycin alone has no effect. Thus, these compounds provide an entirely new class of targeted chemotherapy agents with application, depending on the nature of the targeting moiety, to treatment of a variety of different forms of cancer. Such agents can further be used to promote selective degradation of proteins associated with the pathogenesis of others diseases, including antigens associated with autoimmune disorders and pathogenic proteins associated with Alzheimer's disease. Exemplary targeting moieties which may be employed in compounds of the invention include testosterone, estradiol, tamoxifen and wortmannin.

40 Claims, 20 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 12

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. D

☐ 15. Document ID: US 6660763 B2

L1: Entry 15 of 36 File: USPT Dec 9, 2003

US-PAT-NO: 6660763
DOCUMENT-IDENTIFIER: US 6660763 B2

TITLE: Bis-indolylquinone compounds

DATE-ISSUED: December 9, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Tang; Peng Cho	Moraga	CA		
McMahon; Gerald	San Francisco	CA		
Harris, Jr.; G. Davis	San Francisco	CA		
Lipson; Ken	San Mateo	CA		

US-CL-CURRENT: 514/414; 548/455

ABSTRACT:

The present invention relates to a class of indolylquinone compounds that inhibit GRB-2 adaptor protein function, pharmaceutical compositions comprising these compounds, and methods for ameliorating the symptoms of cell proliferative disorders associated with GRB-2 adaptor protein function using these compounds. The present invention further relates to methods for treating insulin-related disorders, such as diabetes, insulin resistance, insulin deficiency and insulin allergy, and for ameliorating the symptoms of insulin-related disorders, using certain indolylquinone compounds and pharmaceutical compositions thereof. The present invention also relates to novel synthetic methods for the preparation of mono- and bis-indolylquinone compounds.

4 Claims, 1 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 1

☐ 16. Document ID: US 6639055 B1

L1: Entry 16 of 36 File: USPT Oct 28, 2003

US-PAT-NO: 6639055
DOCUMENT-IDENTIFIER: US 6639055 B1

TITLE: Method for making humanized antibodies

DATE-ISSUED: October 28, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Carter; Paul J.	San Francisco	CA		
Presta; Leonard G.	San Francisco	CA		

US-CL-CURRENT: 530/387.3; 424/130.1, 530/387.1, 530/388.1

ABSTRACT:

Variant immunoglobulins, particularly humanized antibody polypeptides are provided, along with methods for their preparation and use. Consensus immunoglobulin sequences and structural models are also provided.

3 Claims, 9 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 9

☐ 17. Document ID: US 6635482 B1

L1: Entry 17 of 36 File: USPT Oct 21, 2003

US-PAT-NO: 6635482
DOCUMENT-IDENTIFIER: US 6635482 B1
**** See image for Certificate of Correction ****

TITLE: Monoclonal antibodies to membrane neutrokine-.alpha.

DATE-ISSUED: October 21, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Yu; Guo-Liang	Berkeley	CA		
Ebner; Reinhard	Gaithersburg	MD		
Ni; Jian	Rockville	MD		
Rosen; Craig A.	Laytonsville	MD		

US-CL-CURRENT: 435/326; 435/328, 435/331, 435/4, 530/387.1, 530/387.3, 530/387.9, 530/388.1, 530/388.15

ABSTRACT:

The present invention relates to a novel Neutrokine-alpha, and a splice variant thereof designated Neutrokine-alphaSV, polynucleotides and polypeptides which are members of the TNF family. In particular, isolated nucleic acid molecules are provided encoding the human Neutrokine-alpha and/or Neutrokine-alphaSV polypeptides, including soluble forms of the extracellular domain. Neutrokine-alpha and/or Neutrokine-alphaSV polypeptides are also provided as are vectors, host cells and recombinant methods for producing the same. The invention further relates to screening methods for identifying agonists and antagonists of Neutrokine-alpha and/or Neutrokine-alphaSV activity. Also provided are diagnostic methods for detecting immune system-related disorders and therapeutic methods for treating immune system-related disorders.

32 Claims, 34 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 22

☐ 18. Document ID: US 6589758 B1

L1: Entry 18 of 36 File: USPT Jul 8, 2003

US-PAT-NO: 6589758
DOCUMENT-IDENTIFIER: US 6589758 B1

TITLE: Crystal of a kinase-ligand complex and methods of use

DATE-ISSUED: July 8, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Zhu; Xiaotian	Watertown	MA		

US-CL-CURRENT: 435/15; 435/4, 530/350

ABSTRACT:

The invention relates to the three-dimensional structure of a crystal of a kinase enzyme complexed with a ligand. The three-dimensional structure of a protein kinase-ligand complex is disclosed. The invention also relates to methods of preparing such crystals. Kinase-ligand crystal structures wherein the ligand is an inhibitor molecule are useful for providing structural information that may be integrated into drug screening and drug design processes. Thus, the invention also relates to methods of using the crystal structure of kinase enzyme-ligand complexes for identifying, designing, selecting, or testing inhibitors of kinase enzymes, such inhibitors being useful as therapeutics for the treatment or modulation of i) diseases; ii) disease symptoms; or iii) the effect of other physiological events mediated by kinases; having one or more kinase enzymes involved in their pathology.

36 Claims, 32 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 13

☐ 19. Document ID: US 6562579 B1

L1: Entry 19 of 36 File: USPT May 13, 2003

US-PAT-NO: 6562579
DOCUMENT-IDENTIFIER: US 6562579 B1
**** See image for Certificate of Correction ****

TITLE: Diagnostic methods using antibodies to Neutrokine-alpha

DATE-ISSUED: May 13, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Yu; Guo-Liang	Berkeley	CA		

Ebner; Reinhard	Gaithersburg	MD
Ni; Jian	Rockville	MD
Rosen; Craig A.	Laytonsville	MD

US-CL-CURRENT: 435/7.1; 435/7.2, 530/350, 530/387.9, 530/388.1, 530/388.23, 530/389.1, 530/391.3

ABSTRACT:

The present invention relates to a novel Neutrokine-alpha, and a splice variant thereof designated Neutrokine-alphaSV, polynucleotides and polypeptides which are members of the TNF family. In particular, isolated nucleic acid molecules are provided encoding the human Neutrokine-alpha and/or Neutrokine-alphaSV polypeptides, including soluble forms of the extracellular domain. Neutrokine-alpha and/or Neutrokine-alphaSV polypeptides are also provided as are vectors, host cells and recombinant methods for producing the same. The invention further relates to screening methods for identifying agonists and antagonists of Neutrokine-alpha and/or Neutrokine-alphaSV activity. Also provided are diagnostic methods for detecting immune system-related disorders and therapeutic methods for treating immune system-related disorders.

28 Claims, 33 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 22

☐ 20. Document ID: US 6541615 B1

L1: Entry 20 of 36 File: USPT Apr 1, 2003

US-PAT-NO: 6541615
DOCUMENT-IDENTIFIER: US 6541615 B1

TITLE: SIRP proteins and uses thereof

DATE-ISSUED: April 1, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Ullrich; Axel	Munchen			DE
Kharitonenkov; Alexei	Carmel	IN		
Chen; Zhengiun	Graefelfing			DE

US-CL-CURRENT: 536/23.1; 435/320.1, 435/325, 435/455, 435/6, 435/7.1, 530/300, 530/350, 536/23.6, 800/8

ABSTRACT:

The present invention features isolated, purified, or enriched nucleic acid encoding a SIRP polypeptide and isolated, purified, or enriched SIRP polypeptide and uses thereof.

17 Claims, 3 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. D

☐ 21. Document ID: US 6500654 B1

L1: Entry 21 of 36 File: USPT Dec 31, 2002

US-PAT-NO: 6500654
DOCUMENT-IDENTIFIER: US 6500654 B1
**** See image for Certificate of Correction ****

TITLE: CARK protein and nucleic acid molecules and uses therefor

DATE-ISSUED: December 31, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Raju; Jeyaseelan	Acton	MA		

US-CL-CURRENT: 435/194; 435/183, 435/69.2, 536/23.2

ABSTRACT:

The invention provides isolated nucleic acids molecules, designated CARK nucleic acid molecules. The invention also provides antisense nucleic acid molecules, recombinant expression vectors containing CARK nucleic acid molecules, host cells into which the expression vectors have been introduced, and nonhuman transgenic animals in which a CARK gene has been introduced or disrupted. The invention still further provides isolated CARK proteins, fusion proteins, antigenic peptides and anti-CARK antibodies. Diagnostic methods utilizing compositions of the invention are also provided.

17 Claims, 31 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 31

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. D

☐ 22. Document ID: US 6495558 B1

L1: Entry 22 of 36 File: USPT Dec 17, 2002

US-PAT-NO: 6495558
DOCUMENT-IDENTIFIER: US 6495558 B1
**** See image for Certificate of Correction ****

TITLE: Kinase inhibitors

DATE-ISSUED: December 17, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Armistead; David M.	Sudbury	MA		
Bemis; Jean E.	Arlington	MA		
Elbaum; Daniel	Newton	MA		
Habgood; Gregory J.	Merrimac	MA		
Novak; Perry M.	Milford	MA		
Nunes; Joseph J.	Andover	MA		
Toledo-Sherman; Leticia M.	Somerville	MA		

US-CL-CURRENT: 514/272; 544/321

ABSTRACT:

The invention relates to inhibitors of kinases, compositions comprising the inhibitors, and methods of using the inhibitors and inhibitor compositions. The inhibitors and compositions comprising them are useful for treating disease or disease symptoms. The invention also provides for methods of making kinase inhibitor compounds, methods of inhibiting kinase activity, and methods for treating disease or disease symptoms.

5 Claims, 0 Drawing figures
Exemplary Claim Number: 1

☐ 23. Document ID: US 6495556 B2

L1: Entry 23 of 36 File: USPT Dec 17, 2002

US-PAT-NO: 6495556
DOCUMENT-IDENTIFIER: US 6495556 B2
**** See image for Certificate of Correction ****

TITLE: Dimethoxy quinazolines for treating diabetes

DATE-ISSUED: December 17, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Leak	MN		
Sudbeck; Elise A.	St. Paul	MN		
Cetkovic; Marina	Maplewood	MN		
Malaviya; Ravi	Shoreview	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.4

ABSTRACT:

The invention provides novel JAK-3 inhibitors that are useful for treating leukemia and lymphoma. The compounds are also useful to treat or prevent skin cancer, as well as sunburn and UVB-induced skin inflammation. In addition, the compounds of the present invention prevent the immunosuppressive effects of UVB radiation, and are useful to treat or prevent autoimmune diseases, inflammation, and transplant rejection. The invention also provides pharmaceutical compositions comprising compounds of the invention, as well as therapeutic methods for their use.

1 Claims, 70 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 55

☐ 24. Document ID: US 6482605 B1

L1: Entry 24 of 36 File: USPT Nov 19, 2002

US-PAT-NO: 6482605
DOCUMENT-IDENTIFIER: US 6482605 B1
**** See image for Certificate of Correction ****

TITLE: Protein tyrosine phosphatase PTP20 and related products and methods

DATE-ISSUED: November 19, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Aoki; Naohito	Nagoya			JP
Ullrich; Axel	Martimiried			DE

US-CL-CURRENT: 435/21; 435/194, 435/252.3, 435/320.1, 530/350, 536/23.2

ABSTRACT:

The present invention relates to a novel polypeptide, PTP20, and to nucleic acid molecules encoding the polypeptide . The invention also relates to nucleic acid molecules encoding portions of the phosphatase, nucleic acid vectors containing PTP20 related nucleic acid molecules, recombinant cells containing such nucleic acid vectors, polypeptides purified from such recombinant cells, antibodies to such polypeptides, and methods of identifying compounds that bind PTP20 or abrogate its interactions with natural binding partners. Also disclosed are methods for diagnosing abnormal conditions in an organism with PTP20 related molecules or compounds.

11 Claims, 0 Drawing figures
Exemplary Claim Number: 1

☐ 25. Document ID: US 6469013 B2

L1: Entry 25 of 36 File: USPT Oct 22, 2002

US-PAT-NO: 6469013
DOCUMENT-IDENTIFIER: US 6469013 B2
** See image for Certificate of Correction **

TITLE: Therapeutic compounds

DATE-ISSUED: October 22, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Sudbeck; Elise A.	St. Paul	MN		
Cetkovic; Marina	Maplewood	MN		
Malaviya; Ravi	Shoreview	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.3; 514/266.4

ABSTRACT:

The invention provides novel JAK-3 inhibitors that are useful for treating leukemia and lymphoma. The compounds are also useful to treat or prevent skin cancer, as well as sunburn and UVB-induced skin inflammation. In addition, the compounds of the present invention prevent the immunosuppressive effects of UVB radiation, and are useful to treat or prevent autoimmune diseases, inflammation, and transplant rejection. The invention also provides pharmaceutical compositions comprising compounds of the invention, as well as therapeutic methods for their use.

3 Claims, 70 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 55

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. D

☐ 26. Document ID: US 6465507 B2

L1: Entry 26 of 36 File: USPT Oct 15, 2002

US-PAT-NO: 6465507
DOCUMENT-IDENTIFIER: US 6465507 B2

TITLE: 3-(pyrolyllactone)-2-indolinone compounds as kinase inhibitors

DATE-ISSUED: October 15, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY

Tang; Peng Cho	Moraga	CA
Miller; Todd A.	Bend	OR
Li; Xiaoyuan	San Jose	CA
Zhang; Ruofei	Foster City	CA
Cui; Jinrong	Albany	CA
Huang; Ping	Mountain View	CA
Wei; Chung Chun	Foster City	CA

US-CL-CURRENT: 514/265.1; 514/215, 514/248, 514/249, 514/300, 540/580, 544/236, 544/280, 544/350, 546/113, 548/455

ABSTRACT:

The invention relates to certain indolinone compounds, their method of synthesis, and a combinatorial library consisting of the indolinone compounds of the invention. The invention also relates to methods of modulating the function of protein kinases using indolinone compounds of the invention and methods of treating diseases by modulating the function of protein kinases and related signal transduction pathways.

15 Claims, 0 Drawing figures
Exemplary Claim Number: 1

☐ 27. Document ID: US 6403770 B1

L1: Entry 27 of 36 File: USPT Jun 11, 2002

US-PAT-NO: 6403770
DOCUMENT-IDENTIFIER: US 6403770 B1
**** See image for Certificate of Correction ****

TITLE: Antibodies to neutrokine-alpha

DATE-ISSUED: June 11, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Yu; Guo-Liang	Berkeley	CA		
Ebner; Reinhard	Gaithersburg	MD		
Ni; Jian	Rockville	MD		
Rosen; Craig A.	Laytonsville	MD		

US-CL-CURRENT: 530/387.3; 435/69.5, 435/7.1, 530/300, 530/324, 530/351, 530/388.1, 530/388.23

ABSTRACT:

The present invention relates to a novel Neutrokine-alpha, and a splice variant thereof designated Neutrokine-alphaSV, polynucleotides and polypeptides which are

members of the TNF family. In particular, isolated nucleic acid molecules are provided encoding the human Neutrokine-alpha and/or Neutrokine-alphaSV polypeptides, including soluble forms of the extracellular domain. Neutrokine-alpha and/or Neutrokine-alphaSV polypeptides are also provided as are vectors, host cells and recombinant methods for producing the same. The invention further relates to screening methods for identifying agonists and antagonists of Neutrokine-alpha and/or Neutrokine-alphaSV activity. Also provided are diagnostic methods for detecting immune system-related disorders and therapeutic methods for treating immune system-related disorders.

292 Claims, 11 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 22

☐ 28. Document ID: US 6391874 B1

L1: Entry 28 of 36 File: USPT May 21, 2002

US-PAT-NO: 6391874
DOCUMENT-IDENTIFIER: US 6391874 B1

TITLE: Fused heterocyclic compounds as protein tyrosine kinase inhibitors

DATE-ISSUED: May 21, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Cockerill; George Stuart	Herts			GB
Carter; Malcolm Clive	Herts			GB
Guntrip; Stephen Barry	Herts			GB
Smith; Kathryn Jane	Herts			GB

US-CL-CURRENT: 514/233.5; 514/252.17, 514/266.2, 514/266.22, 514/312, 544/107, 544/253, 544/363, 546/153

ABSTRACT:

Substituted heteroaromatic compounds of formula (I) and in particular substituted quinolines and quinazolines, are protein tyrosine kinase inhibitors. The compounds are described as are methods for their preparation, pharmaceutical compositions including such compounds and their use in medicine, for example in the treatment of cancer and psoriasis, or a salt or solvate thereof; wherein X is N or CH; Y is a group W(CH.sub.2), (CH.sub.2)W, or W, in which W is O, S(O).sub.m wherein m is 0, 1 or 2, or NR.sup.a wherein R.sup.a is hydrogen or a C.sub.1-8 alkyl group; R.sup.1 represents a phenyl group or a 5- or 6-membered heterocyclic ring containing 1 to 4 heteroatoms selected from N, O or S(O).sub.m, wherein m is as defined above, with the provisos that the ring does not contain two adjacent O or S(O).sub.m atoms and that where the ring contains only N as heteroatom(s) the ring is C-linked to the quinazoline or quinoline ring, R.sup.1 being optionally substituted by one or more R.sup.3 ;groups; P=0 to 3; U, R.sup.2, R.sup.3 are as defined in the application. ##STR1##

32 Claims, 0 Drawing figures
Exemplary Claim Number: 1

☐ 29. Document ID: US 6376529 B1

L1: Entry 29 of 36 File: USPT Apr 23, 2002

US-PAT-NO: 6376529
DOCUMENT-IDENTIFIER: US 6376529 B1

TITLE: Mono- and bis-indolylquinones and prophylactic and therapeutic uses thereof

DATE-ISSUED: April 23, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Tang; Peng Cho	Moraga	CA	94556	
McMahon; Gerald	San Francisco	CA	94109	
Harris, Jr.; G. Davis	San Francisco	CA	94114	
Lipson; Ken	San Mateo	CA	94402	

US-CL-CURRENT: 514/414; 548/455, 548/460

ABSTRACT:

The present invention relates to a class of indolylquinone compounds that inhibit GRB-2 adaptor protein function, pharmaceutical compositions comprising these compounds, and methods for ameliorating the symptoms of cell proliferative disorders associated with GRB-2 adaptor protein function using these compounds. The present invention further relates to methods for treating insulin-related disorders, such as diabetes, insulin resistance, insulin deficiency and insulin allergy, and for ameliorating the symptoms of insulin-related disorders, using certain indolylquinone compounds and pharmaceutical compositions thereof. The present invention also relates to novel synthetic methods for the preparation of mono- and bis-indolylquinone compounds.

34 Claims, 1 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 1

☐ 30. Document ID: US 6313129 B1

L1: Entry 30 of 36 File: USPT Nov 6, 2001

US-PAT-NO: 6313129
DOCUMENT-IDENTIFIER: US 6313129 B1

TITLE: Therapeutic compounds

DATE-ISSUED: November 6, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uckun; Fatih M.	White Bear Lake	MN		
Sudbeck; Elise A.	St. Paul	MN		
Cetkovic; Marina	Maplewood	MN		
Malaviya; Ravi	Shoreview	MN		
Liu; Xing-Ping	Minneapolis	MN		

US-CL-CURRENT: 514/266.3; 514/266.4

ABSTRACT:

The invention provides novel JAK-3 inhibitors that are useful for treating leukemia and lymphoma. The compounds are also useful to treat or prevent skin cancer, as well as sunburn and UVB-induced skin inflammation. In addition, the compounds of the present invention prevent the immunosuppressive effects of UVB radiation, and are useful to treat or prevent autoimmune diseases, inflammation, and transplant rejection. The invention also provides pharmaceutical compositions comprising compounds of the invention, as well as therapeutic methods for their use.

9 Claims, 42 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 55

Terms	Documents
(protein tyrosine kinase adj3 2 or Pyk adj3 2) and crystal	36

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Search Results - Record(s) 31 through 36 of 36 returned.

☐ 31. Document ID: US 6261818 B1

L1: Entry 31 of 36 File: USPT Jul 17, 2001

US-PAT-NO: 6261818
DOCUMENT-IDENTIFIER: US 6261818 B1

TITLE: CARK protein and nucleic acid molecules and uses therefor

DATE-ISSUED: July 17, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Raju; Jeyaseelan	Acton	MA		

US-CL-CURRENT: 435/194; 435/15, 435/252.3, 435/320.1, 435/325, 435/6, 435/69.1, 536/23.1, 536/23.2

ABSTRACT:

The invention provides isolated nucleic acids molecules, designated CARK nucleic acid molecules. The invention also provides antisense nucleic acid molecules, recombinant expression vectors containing CARK nucleic acid molecules, host cells into which the expression vectors have been introduced, and nonhuman transgenic animals in which a CARK gene has been introduced or disrupted. The invention still further provides isolated CARK proteins, fusion proteins, antigenic peptides and anti-CARK antibodies. Diagnostic methods utilizing compositions of the invention are also provided.

110 Claims, 4 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 17

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw D

☐ 32. Document ID: US 6174889 B1

L1: Entry 32 of 36 File: USPT Jan 16, 2001

US-PAT-NO: 6174889
DOCUMENT-IDENTIFIER: US 6174889 B1
** See image for Certificate of Correction **

TITLE: Bicyclic heteroaromatic compounds as protein tyrosine kinase inhibitors

DATE-ISSUED: January 16, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Cockerill; George Stuart	Bedford			GB
Carter; Malcolm Clive	Ware			GB
Guntrip; Stephen Barry	Hertford			GB
Smith; Kathryn Jane	Bishop's Stortford			GB

US-CL-CURRENT: 514/264.1; 514/252.02, 514/255.05, 514/264.11, 544/238, 544/279

ABSTRACT:

Substituted heteroaromatic compounds, and in particular substituted bicyclic heteroaromatic compounds of formula (I), wherein X is N or CH; A represents a fused 5, 6 or 7-membered heterocyclic ring containing 1 to 5 heteroatoms which may be the same or different and which are selected from N, O or S(O).sub.m, wherein m is as defined above, the heterocyclic ring containing a total of 1, 2 or 3 double bonds inclusive of the bond in the pyridine or pyrimidine ring to which it is fused, with the provisos that the heterocyclic ring does not form part of a purine and that the fused heterocyclic ring does not contain two adjacent O or S(O).sub.m atoms. U represents a 5 to 10-membered mono or bicyclic ring system in which one or more of the carbon atoms is optionally replaced by a heteroatom independently selected from N, O and S(O).sub.m, wherein m is 0, 1 or 2 and wherein the ring system is substituted by at least one independently selected R.sup.6 group and is optionally substituted by at least one independently selected R.sup.4 group, with the proviso that U does not represent phenyl; are protein tyrosine kinase inhibitors. The compounds are described as are methods for their preparation, pharmaceutical compositions including such compounds and their use in medicine, for example in the treatment of cancer and psoriasis. ##STR1##

25 Claims, 0 Drawing figures
Exemplary Claim Number: 1

☐ 33. Document ID: US 6100254 A

L1: Entry 33 of 36 File: USPT Aug 8, 2000

US-PAT-NO: 6100254
DOCUMENT-IDENTIFIER: US 6100254 A
**** See image for Certificate of Correction ****

TITLE: Inhibitors of protein tyrosine kinases

DATE-ISSUED: August 8, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY

Budde; Raymond J. A.	Bellaire	TX
Ellman; Jonathan A.	Oakland	CA
Levin; Victor A.	Houston	TX
Gallick; Gary E.	Kingwood	TX
Newman; Robert A.	Sugar Land	TX

US-CL-CURRENT: 514/221; 540/504, 540/506, 540/507, 540/508, 540/509, 540/510, 540/511, 540/512, 540/513, 540/514

ABSTRACT:

Disclosed herein are small molecule, non-peptidyl inhibitors of protein tyrosine kinases, and methods for their use. The instant inhibitors are based on a 1,4-benzodiazepin-2-one nucleus. Methods are provided for inhibition of specific protein tyrosine kinases, for example pp60.sup.c-src. Methods are further provided for the use of these inhibitors in situations where the inhibition of a protein tyrosine kinase is indicated, for example, in the treatment of certain diseases in mammals, including humans.

31 Claims, 7 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 7

☐ 34. Document ID: US 5955259 A

L1: Entry 34 of 36 File: USPT Sep 21, 1999

US-PAT-NO: 5955259
DOCUMENT-IDENTIFIER: US 5955259 A

TITLE: Method for assessing modulation of potassium ion channel activity

DATE-ISSUED: September 21, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Holmes; Todd C.	Somerville	MA		
Levitan; Irwin B.	Newton	MA		

US-CL-CURRENT: 435/4; 435/7.1, 435/7.8

ABSTRACT:

The present invention relates to a method for assessing the ability of a compound to modulate the formation of a complex between a potassium channel and a protein tyrosine kinase. The method comprises the steps of (1) contacting a first polypeptide comprising the proline-rich binding region of the potassium channel, a second protein comprising the SH3 binding domain of the protein tyrosine kinase and the compound to be assessed; and (2) measuring the extent of complex formation between the first polypeptide and the second polypeptide.

6 Claims, 1 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. D

☐ 35. Document ID: US 5912183 A

L1: Entry 35 of 36 File: USPT Jun 15, 1999

US-PAT-NO: 5912183
DOCUMENT-IDENTIFIER: US 5912183 A

TITLE: Peptide inhibitors of mitogenesis and motogenesis

DATE-ISSUED: June 15, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Comoglio; Paolo	Turin			IT
Ponzetto; Carola	Turin			IT

US-CL-CURRENT: 436/501; 530/300, 530/324, 530/326

ABSTRACT:

The invention in the field of cell biology relates to novel peptides able to interact with intracellular signal transducers, thus interfering with signal transduction pathways leading to cell proliferation and motility.

The peptides of the invention may be chemically synthesized from single amino acids and/or preformed peptides of two or more amino acid residues.

The peptides of the invention find an useful application in the treatment of a neoplastic disease.

14 Claims, 39 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 18

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. D

☐ 36. Document ID: EP 1627045 A2, WO 2004078923 A2, US 20050170431 A1

L1: Entry 36 of 36 File: DWPI Feb 22, 2006

DERWENT-ACC-NO: 2004-699356
DERWENT-WEEK: 200615

TITLE: Crystalline form of kinase domain of protein tyrosine kinase 2 (PYK2),

useful for identifying potential PYK2 binding compounds that are useful in treating PYK2 associated diseases such as cancer or inflammation

INVENTOR: IBRAHIM, P; KRUPA, H ; KUMAR, A ; MILBURN, M ; SUZUKI, Y ; KRUPKA, H ; MILBURN, M V

PRIORITY-DATA: 2003US-451101P (February 28, 2003), 2004US-0789818 (February 27, 2004)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
EP 1627045 A2	February 22, 2006	E	000	C12N001/00
WO 2004078923 A2	September 16, 2004	E	237	C12N000/00
US 20050170431 A1	August 4, 2005		000	G01N033/53

INT-CL (IPC): C07 K 16/40; C12 N 0/00; C12 N 1/00; G01 N 33/53

ABSTRACTED-PUB-NO: WO2004078923A
BASIC-ABSTRACT:

NOVELTY - A crystalline form of kinase domain (Ia) of protein tyrosine kinase 2 (PYK2), is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) obtaining (M1) improved ligands binding to PYK2, by:

(a) identifying a compound that binds to PYK2;

(b) determining if the compound interacts with one or more of PYK2 residues, 503, 505, 457, 488, 567, and 554; and

(c) determining if a derivative of the compound binds to PYK2 with greater affinity or greater specificity or both than the compound, where binding with greater affinity or greater specificity or both indicates that the derivative is an improved ligand;

(2) developing (M2) ligands specific for PYK2, by identifying a compound that binds to several of kinases, and determining if a derivative of the compound has greater specificity for PYK2 than the compound;

(3) obtaining (M3) a crystal of PYK2, by subjecting PYK2 protein at 5-20 mg/ml to crystallization condition equivalent to 2-10 % polyethylene glycol (PEG) 8000, 0.2 M sodium acetate, 0.1 % sodium cacodylate pH 6.5, 20 % glycerol;

(4) co-crystal (II) of PYK2 and a PYK2 binding compound;

(5) obtaining (M4) co-crystals of PYK2 with the binding compound, by subjecting PYK2 protein at 5-20 mg/ml to crystallization conditions 2-10 % PEG 8000, 0.2 M sodium acetate, 0.1 % sodium cacodylate pH 6.5, 20 % glycerol in the presence of binding compound;

(6) determining (M5) a structure of a kinase, by creating a homology model from an electronic representation of a PYK2 structure;

(7) an electronic representation (III) of a crystal structure of PYK2;

(8) an electronic representation (IV) of a binding site of PYK2;

(9) an electronic representation (V) of a PYK2 based homology model for a kinase;

(10) identifying a ligand binding to PYK2, by determining if a derivative compound that includes a core structure of formula I (representing triazole derivative) binds to PYK2 with altered binding affinity or specificity or both as compared to the parent compound;

(11) treating (M6) a patient suffering from a disease or condition characterized by abnormal PYK2 activity, by administering a compound (CD) that interacts with three or more of PYK2 residues 503, 505, 457, 488, 567 and 554;

(12) an electronic representation (VI) of an modified PYK2 crystal structure, comprising an electronic representation of the atomic coordinates of a modified PYK2;

(13) attaching (M7) a PYK2 binding compound to an attachment component, by identifying energetically allowed sites for attachment of a the attachment component on a kinase binding compound, and attaching the compound or its derivatives to the attachment component at the energetically allowed site;

(14) a modified compound (VII), comprising a compound of formula I, with a linker moiety attached to it at an energetically allowed site for binding of the modified compound to PYK2; and

(15) developing (M8) a ligand for a kinase comprising conserved residues matching one or more of PYK2 residues 503, 505, 457, 488, 567 and 554, by determining if a compound of formula I binds to the kinase and interacts with the residue.

R1 = H, NR16R17, trifluoromethyl, or lower alkyl, or lower alkenyl, lower alkynyl, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl, all optionally substituted ;

R2 = H, -C(X)R20, C(X)N R16R17, or -S(O2)R21 or lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl, all optionally substituted;

R3 = H, or trifluoromethyl, or alkoxyl, thioalkoxy, amine, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl, all optionally substituted;

R16 and R17 = H, or lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl, all optionally substituted;

R20 = hydroxyl, or lower alkoxy, amine, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl, all optionally substituted; and

R21 = lower alkoxy, amine, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl, all optionally substituted.

ACTIVITY - Cytostatic; Antiinflammatory.

MECHANISM OF ACTION - Modulator of PYK2.

No biological data is given.

USE - (Ia) is useful for modulating PYK2 activity, which involves contacting PYK2

with a compound that binds to PYK2 and interacts with three or more of residues 503, 505, 457, 488, 567 and 554. The compound is at a concentration of 200 micro m or less. (Ia) is also useful for developing a biological agent, which involves analyzing a PYK2 crystal structure and identifying at least one sub-structure for forming the biological agent. The sub substructure comprises an epitope, and the method further involves developing antibodies against the epitope. The sub-structure comprises a mutation site expected to provide altered activity, and the method further involves creating a mutation at the site, thus providing a modified PYK2. The sub-structure comprises an attachment point for attaching a separate moiety. The separate moiety is chosen from peptide, a polypeptide, a solid phase material, a linker, and a label. The method further involves attaching the separate moiety. (II) and (IV) are useful for identifying compounds binding to PYK2, which involves determining the orientation of at least one compound bound with PYK2 in co-crystals of PYK2 with the compound. The compound is identified as a molecular scaffold if it binds weakly to PYK2 and has a molecular weight less than 350 daltons. The method further involves identifying chemical structures of the molecular scaffolds, that, when modified, alter the binding affinity or binding specificity or both between the molecular scaffold and PYK2. The method further involves synthesizing a ligand, where one or more of the chemical structures of the molecular scaffold is modified to provide a ligand that binds to PYK2 with altered binding affinity or binding specificity or both. The molecular scaffold binds to several of kinases. The molecular scaffold interacts with one or more of PYK2 residues 503, 505, 457, 488, 567, and 554. The method further involves modifying a computer representation of a compound complexed with PYK2 by the deletion or addition or both of one or more chemical groups, fitting a computer representation of a compound from a computer database with a computer representation of the active site of PYK2, and identifying compounds that best fit the active site based on geometric fit and energetically favorable complementary interactions as potential binding compounds. (M6) is useful for treating a patient suffering from a disease or condition associated with abnormal PYK2 activity, such as cancer or inflammatory disease or condition (all claimed).

Terms	Documents
(protein tyrosine kinase adj3 2 or Pyk adj3 2) and crystal	36

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☐ 1. Document ID: US 6828320 B2

L9: Entry 1 of 7 File: USPT Dec 7, 2004

US-PAT-NO: 6828320
DOCUMENT-IDENTIFIER: US 6828320 B2

TITLE: Heterocyclic compounds

DATE-ISSUED: December 7, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Cockerill; George Stuart	Bedford			GB
Carter; Malcolm Clive	Ware			GB
Guntrip; Stephen Barry	Hertford			GB
Smith; Kathryn Jane	Bishop's Stortford			GB

US-CL-CURRENT: 514/233.5; 514/312

ABSTRACT:

Substituted heteroaromatic compounds, and in particular substituted quinolines and quinazolines, are protein tyrosine kinase inhibitors. The compounds are described as are methods for their preparation, pharmaceutical compositions including such compounds and their use in medicine, for example in the treatment of cancer and psoriasis.

23 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. D

☐ 2. Document ID: US 6723726 B1

L9: Entry 2 of 7 File: USPT Apr 20, 2004

US-PAT-NO: 6723726
DOCUMENT-IDENTIFIER: US 6723726 B1

TITLE: Protein tyrosine kinase inhibitors

DATE-ISSUED: April 20, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Cockerill; George Stuart	Bedford			GB
Carter; Malcolm Clive	Ware			GB
Guntrip; Stephen Barry	Hertford			GB
Smith; Kathryn Jane	Bishop's Stortford			GB

US-CL-CURRENT: 514/259.41; 514/252.02, 514/255.05, 544/238, 544/278

ABSTRACT:

Substituted heteroaromatic compounds, and in particular substituted bicyclic heteroaromatic compounds of formula (I), wherein X is N or CH; A represents a fused 5, 6 or 7-membered heterocyclic ring containing 1 to 5 heteroatoms which may be the same or different and which are selected from N, O or S(O).sub.m, wherein m is as defined above, the heterocyclic ring containing a total of 1, 2 or 3 double bonds inclusive of the bond in the pyridine or pyrimidine ring to which it is fused, with the provisos that the heterocyclic ring does not form part of a purine and that the fused heterocyclic ring does not contain two adjacent O or S(O).sub.m atoms. U represents a 5 to 10-membered mono or bicyclic ring system in which one or more of the carbon atoms is optionally replaced by a heteroatom independently selected from N, O and S(O).sub.m, wherein m is 0,1 or 2 and wherein the ring system is substituted by at least one independently selected R.sup.6 group and is optionally substituted by at least one independently selected R.sup.4 group, with the proviso that U does not represent phenyl; are protein tyrosine kinase inhibitors. The compounds are described as are methods for their preparation, pharmaceutical compositions including such compounds and their use in medicine, for example in the treatment of cancer and psoriasis.

15 Claims, 0 Drawing figures
Exemplary Claim Number: 1

☐ 3. Document ID: US 6673908 B1

L9: Entry 3 of 7 File: USPT Jan 6, 2004

US-PAT-NO: 6673908
DOCUMENT-IDENTIFIER: US 6673908 B1

TITLE: Tumor necrosis factor receptor 2

DATE-ISSUED: January 6, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Stanton, Jr.; Vincent P.	Belmont	MA		

US-CL-CURRENT: 536/22.1; 435/6, 435/91.1, 435/91.2, 536/23.1, 536/24.3, 536/24.31,

536/24.33

ABSTRACT:

The present disclosure describes the use of genetic variance information for genes involved in inflammatory or immunologic disease, disorder, or dysfunction. The variance information is indicative of the expected response of a patient to a method of treatment. Methods of determining relevant variance information and additional methods of using such variance information are also described.

10 Claims, 0 Drawing figures
Exemplary Claim Number: 1

☐ 4. Document ID: US 6391874 B1

L9: Entry 4 of 7 File: USPT May 21, 2002

US-PAT-NO: 6391874
DOCUMENT-IDENTIFIER: US 6391874 B1

TITLE: Fused heterocyclic compounds as protein tyrosine kinase inhibitors

DATE-ISSUED: May 21, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Cockerill; George Stuart	Herts			GB
Carter; Malcolm Clive	Herts			GB
Guntrip; Stephen Barry	Herts			GB
Smith; Kathryn Jane	Herts			GB

US-CL-CURRENT: 514/233.5; 514/252.17, 514/266.2, 514/266.22, 514/312, 544/107, 544/253, 544/363, 546/153

ABSTRACT:

Substituted heteroaromatic compounds of formula (I) and in particular substituted quinolines and quinazolines, are protein tyrosine kinase inhibitors. The compounds are described as are methods for their preparation, pharmaceutical compositions including such compounds and their use in medicine, for example in the treatment of cancer and psoriasis, or a salt or solvate thereof; wherein X is N or CH; Y is a group W(CH.sub.2), (CH.sub.2)W, or W, in which W is O, S(O).sub.m wherein m is 0, 1 or 2, or NR.sup.a wherein R.sup.a is hydrogen or a C.sub.1-8 alkyl group; R.sup.1 represents a phenyl group or a 5- or 6-membered heterocyclic ring containing 1 to 4 heteroatoms selected from N, O or S(O).sub.m, wherein m is as defined above, with the provisos that the ring does not contain two adjacent O or S(O).sub.m atoms and that where the ring contains only N as heteroatom(s) the ring is C-linked to the quinazoline or quinoline ring, R.sup.1 being optionally substituted by one or more R.sup.3 ;groups; P=0 to 3; U, R.sup.2, R.sup.3 are as defined in the application. ##STR1##

32 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. D.

☐ 5. Document ID: US 6207669 B1

L9: Entry 5 of 7 File: USPT Mar 27, 2001

US-PAT-NO: 6207669
DOCUMENT-IDENTIFIER: US 6207669 B1

TITLE: Bicyclic heteroaromatic compounds as protein tyrosine kinase inhibitors

DATE-ISSUED: March 27, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Cockerill; George Stuart	Bedford			GB
Carter; Malcolm Clive	Ware			GB
Guntrip; Stephen Barry	Hertford			GB
Smith; Kathryn Jane	Bishop's Stortford			GB

US-CL-CURRENT: 514/264.1; 514/255.05, 544/279

ABSTRACT:

Substituted heteroaromatic compounds, and in particular substituted bicyclic heteroaromatic compounds in which one ring is a pyridine or pyrimidine of formula (I) are protein tyrosine kinase inhibitors. The compounds are described as are methods for their preparation, pharmaceutical compositions including such compounds and their use in medicine, for example in the treatment of cancer and psoriasis.
##STR1##

29 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. D.

☐ 6. Document ID: US 6174889 B1

L9: Entry 6 of 7 File: USPT Jan 16, 2001

US-PAT-NO: 6174889
DOCUMENT-IDENTIFIER: US 6174889 B1
** See image for Certificate of Correction **

TITLE: Bicyclic heteroaromatic compounds as protein tyrosine kinase inhibitors

DATE-ISSUED: January 16, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Cockerill; George Stuart	Bedford			GB
Carter; Malcolm Clive	Ware			GB
Guntrip; Stephen Barry	Hertford			GB
Smith; Kathryn Jane	Bishop's Stortford			GB

US-CL-CURRENT: 514/264.1; 514/252.02, 514/255.05, 514/264.11, 544/238, 544/279

ABSTRACT:

Substituted heteroaromatic compounds, and in particular substituted bicyclic heteroaromatic compounds of formula (I), wherein X is N or CH; A represents a fused 5, 6 or 7-membered heterocyclic ring containing 1 to 5 heteroatoms which may be the same or different and which are selected from N, O or S(O).sub.m, wherein m is as defined above, the heterocyclic ring containing a total of 1, 2 or 3 double bonds inclusive of the bond in the pyridine or pyrimidine ring to which it is fused, with the provisos that the heterocyclic ring does not form part of a purine and that the fused heterocyclic ring does not contain two adjacent O or S(O).sub.m atoms. U represents a 5 to 10-membered mono or bicyclic ring system in which one or more of the carbon atoms is optionally replaced by a heteroatom independently selected from N, O and S(O).sub.m, wherein m is 0, 1 or 2 and wherein the ring system is substituted by at least one independently selected R.sup.6 group and is optionally substituted by at least one independently selected R.sup.4 group, with the proviso that U does not represent phenyl; are protein tyrosine kinase inhibitors. The compounds are described as are methods for their preparation, pharmaceutical compositions including such compounds and their use in medicine, for example in the treatment of cancer and psoriasis. ##STR1##

25 Claims, 0 Drawing figures
Exemplary Claim Number: 1

☐ 7. Document ID: US 5770603 A

L9: Entry 7 of 7 File: USPT Jun 23, 1998

US-PAT-NO: 5770603
DOCUMENT-IDENTIFIER: US 5770603 A
**** See image for Certificate of Correction ****

TITLE: Quinazoline derivatives

DATE-ISSUED: June 23, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Gibson; Keith Hopkinson	Macclesfield			GB

US-CL-CURRENT: 514/266.24; 544/293

ABSTRACT:

The invention concerns quinazoline derivatives of the formula I ##STR1## wherein n is 1,2 or 3 and each R.sup.2 is independently halogeno, trifluoromethyl or (1-4C) alkyl;

R.sup.1 is (1-4C)alkoxy;

A is (1-4C)alkylene; and

Q is a saturated, monocyclic 4-, 5-, 6- or 7-membered heterocyclic ring containing one or two oxygen heteroatoms, which ring optionally bears up to four (1-4C)alkyl substituents; or a pharmaceutically-acceptable salt thereof;

processes for their preparation, pharmaceutical compositions containing them and the use of their receptor tyrosine kinase inhibitory properties in the treatment of proliferative disease such as cancer.

10 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Terms	Documents
triazol same kinase same inhibitor and tyrosine kinase	7

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FILE 'HOME' ENTERED AT 18:31:07 ON 12 JUN 2006

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=> s (pyk2 or pyk 2 or protein tyrosine kinase (1w) 2) and crystal?
L1            2 FILE MEDLINE
L2           18 FILE CAPLUS
L3            5 FILE SCISEARCH
L4            1 FILE LIFESCI
L5            4 FILE BIOSIS
L6            2 FILE EMBASE

TOTAL FOR ALL FILES
L7           32 (PYK2 OR PYK 2 OR PROTEIN TYROSINE KINASE (1W) 2) AND CRYSTAL?

=> s l7 not 2004-2006/py
TOTAL FOR ALL FILES
L14          12 L7 NOT 2004-2006/PY

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PROCESSING COMPLETED FOR L14
L15           8 DUP REM L14 (4 DUPLICATES REMOVED)

=> d ibib abs 1-8

L15  ANSWER 1 OF 8  BIOSIS  COPYRIGHT (c) 2006 The Thomson Corporation  on STN
ACCESSION NUMBER:   2003:501651  BIOSIS Full-text
DOCUMENT NUMBER:    PREV200300498087
TITLE:              Crystal structure of Pyk2:
                    Scaffold-based discovery of kinase inhibitors.
AUTHOR(S):          Bollag, Gideon [Reprint Author]; Kumar, Abhinav [Reprint
                    Author]; Mandiyan, Valsan [Reprint Author]; Tsai, James
                    [Reprint Author]; Ibrahim, Prabha [Reprint Author]; Zhang,
                    Kam [Reprint Author]; Milburn, Mike [Reprint Author]
CORPORATE SOURCE:   Plexxikon Inc., Berkeley, CA, USA
SOURCE:             Proceedings of the American Association for Cancer Research
                    Annual Meeting, (July 2003) Vol. 44, pp. 690. print.
                    Meeting Info.: 94th Annual Meeting of the American
                    Association for Cancer Research. Washington, DC, USA. July
                    11-14, 2003.
                    ISSN: 0197-016X.
DOCUMENT TYPE:      Conference; (Meeting)
                    Conference; Abstract; (Meeting Abstract)
LANGUAGE:           English
ENTRY DATE:         Entered STN: 29 Oct 2003
                    Last Updated on STN: 29 Oct 2003

L15  ANSWER 2 OF 8  SCISEARCH  COPYRIGHT (c) 2006 The Thomson Corporation  on
     STN
ACCESSION NUMBER:    2003:549690  SCISEARCH Full-text
THE GENUINE ARTICLE: 600ZN
TITLE:               The focal adhesion kinase (FAK) family member PYK2
                     is central for inflammatory crystal-induced
                     chondrocyte activation.
AUTHOR:              Liote F (Reprint); Rose D; Terkeltaub R; Metz D; Liu-Bryan
                     R
CORPORATE SOURCE:    VAMC, San Diego, CA USA; Univ Calif San Diego, San Diego,
                     CA 92103 USA; Hop Lariboisiere, INSERM U349, Ctr Viggo
                     Petersen, F-75475 Paris, France
COUNTRY OF AUTHOR:   USA; France
SOURCE:              ARTHRITIS AND RHEUMATISM, (SEP 2002) Vol. 46, No. 9, Supp.
                     [S], pp. S592-S592.
                     ISSN: 0004-3591.
PUBLISHER:           WILEY-LISS, DIV JOHN WILEY & SONS INC, 111 RIVER ST,
                     HOBOKEN, NJ 07030 USA.
DOCUMENT TYPE:       Conference; Journal
LANGUAGE:            English
REFERENCE COUNT:     0
ENTRY DATE:          Entered STN: 18 Jul 2003
                     Last Updated on STN: 18 Jul 2003
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L15 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:285913 CAPLUS Full-text
DOCUMENT NUMBER: 135:286477
TITLE: Identification of differentially expressed genes in hepatocellular carcinoma with cDNA microarrays
AUTHOR(S): Shirota, Yukihiro; Kaneko, Shuichi; Honda, Masao; Kawai, Hiroshi F.; Kobayashi, Kenichi
CORPORATE SOURCE: First Department of Internal Medicine, School of Medicine, Kanazawa University, Kanazawa, 920-8641, Japan
SOURCE: Hepatology (Philadelphia, PA, United States) (2001), 33(4), 832-840
CODEN: HPTLD9; ISSN: 0270-9139
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Genes expressed in hepatocellular carcinoma (HCC) were analyzed using cDNA microarrays to clarify gene abnormalities in HCC. MRNA was extracted from cancerous and noncancerous tissues of 10 patients with HCC, cDNA labeled with Cy5 and Cy3 fluorescence was prepared, and it was hybridized for each patient with a cDNA microarray consisting of 1080 elements (930 unique genes). The mRNA expression rate of each element in HCC was evaluated using the level of mRNA expression in noncancerous tissue in each patient as a reference The expression of 10 genes was enhanced 2 times or more in HCC cancerous tissue compared with noncancerous tissue in 5 or more of the 10 patients. In contrast, 9 genes were expressed at half the level or less in HCC cancerous tissue compared with noncancerous tissue. When hierarchical clustering was performed to identify genes related to clin. phenotypes of the patients, 22 genes showed changes associated with the degree of differentiation of HCC. Thirteen of these genes were transcriptional factors or tissue-specific expression proteins related to cell differentiation or development. Our present anal. clarified a number of genes that characterize HCC. This information based on examination of clin. samples is considered to be useful for clarification of the mechanism of hepatocarcinogenesis and the diagnosis and treatment of HCC.
REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:84722 CAPLUS Full-text
DOCUMENT NUMBER: 134:278292
TITLE: Functional proteomic analysis of protein kinase C ε signaling complexes in the normal heart and during cardioprotection
AUTHOR(S): Ping, Peipei; Zhang, Jun; Pierce, William M., Jr.; Bolli, Roberto
CORPORATE SOURCE: Dep. Physiology and Biophysics, Univ. Louisville, Louisville, KY, USA
SOURCE: Circulation Research (2001), 88(1), 59-62
CODEN: CIRUAL; ISSN: 0009-7330
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Using two-dimensional electrophoresis, mass spectrometry, immunoblotting, and affinity pull-down assays, we found that myocardial protein kinase C ε (PKCε) is phys. associated with at least 36 known proteins that are organized into structural proteins, signaling mols., and stress-responsive proteins. Furthermore, we found that the cardioprotection induced by activation of PKCε is coupled with dynamic modulation and recruitment of PKCε-associated proteins. The results suggest heretofore-unrecognized functions of PKCE and provide an integrated framework for the understanding of PKCε-dependent signaling architecture and cardioprotection.
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 5 OF 8 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2000069319 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 10601011
TITLE: Crystal structure of the ARF-GAP domain and ankyrin repeats of PYK2-associated protein beta.
AUTHOR: Mandiyan V; Andreev J; Schlessinger J; Hubbard S R
CORPORATE SOURCE: Department of Pharmacology, Skirball Institute of Biomolecular Medicine, New York University Medical School,

New York, NY 10016, USA.
SOURCE: The EMBO journal, (1999 Dec 15) Vol. 18, No. 24, pp. 6890-8.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1DCQ
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 4 Feb 2000
Last Updated on STN: 4 Feb 2000
Entered Medline: 27 Jan 2000

AB ADP ribosylation factors (ARFs), which are members of the Ras superfamily of GTP-binding proteins, are critical components of vesicular trafficking pathways in eukaryotes. Like Ras, ARFs are active in their GTP-bound form, and their duration of activity is controlled by GTPase-activating proteins (GAPs), which assist ARFs in hydrolyzing GTP to GDP. PAPbeta, a protein that binds to and is phosphorylated by the non-receptor tyrosine kinase PYK2, contains several modular signaling domains including a pleckstrin homology domain, an SH3 domain, ankyrin repeats and an ARF-GAP domain. Sequences of ARF-GAP domains show no recognizable similarity to those of other GAPs, and contain a characteristic Cys-X(2)-Cys-X(16-17)-Cys-X(2)-Cys motif. The crystal structure of the PAPbeta ARF-GAP domain and the C-terminal ankyrin repeats has been determined at 2.1 A resolution. The ARF-GAP domain comprises a central three-stranded beta-sheet flanked by five alpha-helices, with a Zn(2+) ion coordinated by the four cysteines of the cysteine-rich motif. Four ankyrin repeats are also present, the first two of which form an extensive interface with the ARF-GAP domain. An invariant arginine and several nearby hydrophobic residues are solvent exposed and are predicted to be the site of interaction with ARFs. Site-directed mutagenesis of these residues confirms their importance in ARF-GAP activity.

L15 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:51280 CAPLUS Full-text
DOCUMENT NUMBER: 128:214922
TITLE: The 2.35 Å crystal structure of the inactivated form of chicken Src: a dynamic molecule with multiple regulatory interactions
AUTHOR(S): Williams, John C.; Weijland, Albert; Gonfloni, Stefania; Thompson, Andy; Courtneidge, Sara A.; Superti-Furga, Giulio; Wierenga, Rik K.
CORPORATE SOURCE: European Molecular Biology Laboratory, Heidelberg, D-69117, Germany
SOURCE: Journal of Molecular Biology (1997), 274(5), 757-775
CODEN: JMOBAK; ISSN: 0022-2836
PUBLISHER: Academic Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The Src protein tyrosine kinase plays a critical role in a variety of signal transduction pathways. Strict regulation of its activity is necessary for proper signaling. We present here the crystal structure of chicken Src which is phosphorylated at Tyr527 and represents its least active form. Our structure, similar to the recently reported human Hck and Src structures, contains the SH3, SH2 and the kinase domains and the C-terminal regulatory tail but not the N-terminal unique domain. The SH3 domain uses its hydrophobic surface to coordinate the SH2-kinase linker such that residues Gln251 and Leu255 specifically interact with side chains in the β2-β3 and the αC-β4 loops of the N-terminal lobe opposite of the kinase active site. This position of the SH3 domain and the coordination of the SH2-kinase linker also optimally places the SH2 domain such that the phosphorylated Tyr527 in the C-terminal tail interacts with the SH2 binding pocket. Analogous to Cdk2 kinase, the position of the Src αC-helix in the N-terminal lobe is swung out disrupting the position of the active site residues. Superposition of other protein kinases including human Hck and Src onto chicken Src indicate that the αC-helix position is affected by the relative position of the N-terminal lobe with respect to the C-terminal lobe of the kinase and that the presence of the SH3/SH2-kinase linker/N-terminal lobe interactions restricts the kinase lobes and αC-helix access to the active conformation. These superpositions also suggest that the highly conserved αC-β4 loop restricts the conformational freedom of the N-terminal lobe by anchoring it to the C-terminal lobe. Finally, based on sequence alignments and conservation of hydrophobic residues in the Src SH2-kinase linker as well as in the αC-β4 and β2-β3 loops, we propose that the Src-related kinases, Abl, Btk and Csk, share the same quaternary structure.

REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 7 OF 8 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1997:667121 SCISEARCH Full-text
THE GENUINE ARTICLE: XU769
TITLE: Phosphotyrosyl-based motifs in the structure-based design of protein-tyrosine kinase-dependent signal transduction inhibitors
AUTHOR: Burke T R (Reprint); Yao Z J; Smyth M S; Ye B
CORPORATE SOURCE: NCI, MED CHEM LAB, DIV BASIC SCI, NIH, BETHESDA, MD 20892
COUNTRY OF AUTHOR: USA
SOURCE: CURRENT PHARMACEUTICAL DESIGN, (JUN 1997) Vol. 3, No. 3, pp. 291-304.
ISSN: 1381-6128.
PUBLISHER: BENTHAM SCIENCE PUBL BV, PO BOX 1673, 1200 BR HILVERSUM, NETHERLANDS.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 176
ENTRY DATE: Entered STN: 1997
Last Updated on STN: 1997

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Transmission of extracellular signals from the cell membrane to the nucleus depends on modification of phosphorylation states of intracellular proteins. Tyrosine, serine and threonine residues are the principal amino acid targets of these phosphorylation events, with tyrosyl residues being particularly important for pathways mediated by growth factors and cytokines. Aberrations in phosphotyrosyl (pTyr)-dependent signalling can contribute to a variety of diseases, including cancers, and for this reason selective modulation of pTyr-dependent signalling may afford new therapeutic approaches. The design of such therapeutics is facilitated by the functional compartmentalization of pTyr dependent signalling into three broad categories: (1) the generation of pTyr residues by protein-tyrosine kinases (PTK); (2) pTyr-dependent protein-protein associations mediated by binding modules such as Src homology 2 (SH2) and phosphotyrosine binding (PTB) domains and (3) the dephosphorylation of pTyr residues by protein-tyrosine phosphatases (PTPs). The pTyr residue itself, which is a unifying component of this signalling triad, potentially affords a starting point for the design of antagonists. In the PTK, SH2/PTB and PTP domain signalling environments, the pTyr residue plays unique roles by participating in interactions characteristic to each. Therefore, depending on which aspects of the L-4'-phosphotyrosyl structure are emphasized, and the manner in which they are utilized, inhibitors can be potentially directed against distinct legs of the signalling triad. This review will provide examples of this, by examining several series of compounds that have been prepared as inhibitors of either PTKs, SH2/PTB domains or PTPs. Also described will be how the pTyr structure can serve as a thematic Rosetta stone for the development of signal transduction inhibitors.

L15 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:205222 CAPLUS Full-text
DOCUMENT NUMBER: 122:26685
TITLE: High-resolution crystal structures of tyrosine kinase SH3 domains complexed with proline-rich peptides
AUTHOR(S): Musacchio, Andrea; Saraste, Matti; Wilmanns, Matthias
CORPORATE SOURCE: European Molecular Biol. Laboratory, Heidelberg, 102209, Germany
SOURCE: Nature Structural Biology (1994), 1(8), 546-51
CODEN: NSBIEW; ISSN: 1072-8368
PUBLISHER: Nature Publishing Co.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB SH3 (Src-homol. 3) domains bind to proline (Pro)-rich motifs in target proteins. Here, high-resolution crystal structures of the complexes between the SH3 domains of gene abl and gene fyn protein tyrosine kinases, and 2 10-residue Pro-rich peptides derived from the SH3-binding proteins, 3BP-1 and 3BP-2, were determined The x-ray data showed that the basic mode of binding of both Pro-rich peptides was the same. The peptides were bound over their entire length and interacted with 3 major sites on the SH3 mols. by both H-bonding and van der Waals contacts. Residues 4-10 of the peptide adopted the conformation

of a left-handed polyproline helix type II. The binding of Pro at position 2 required a kink at non-Pro position 3.

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=> s triazol and tyrosine kinase
TOTAL FOR ALL FILES
L29         83 TRIAZOL AND TYROSINE KINASE

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PROCESSING COMPLETED FOR L29
L30          83 DUP REM L29 (0 DUPLICATES REMOVED)

=> s l29 not 2004-2006/py

TOTAL FOR ALL FILES
L37         31 L29 NOT 2004-2006/PY

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PROCESSING COMPLETED FOR L37
L38          31 DUP REM L37 (0 DUPLICATES REMOVED)

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L38  ANSWER 1 OF 31  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2003:335080  CAPLUS Full-text
DOCUMENT NUMBER:          138:337982
TITLE:                    Preparation of 2-carboxamidopyrroles as
                          tyrosine kinase inhibitors
INVENTOR(S):              Trotter, B. Wesley
PATENT ASSIGNEE(S):       Merck & Co., Inc., USA
SOURCE:                   PCT Int. Appl., 92 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.        DATE
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     WO 2003035619         A1    20030501    WO 2002-US33962        20021023
     WO 2003035619         C1    20030703
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS,
             LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL,
             PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA,
             UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
             FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF,
             CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.:                       US 2001-343000P     P  20011025
OTHER SOURCE(S):          MARPAT 138:337982
GI
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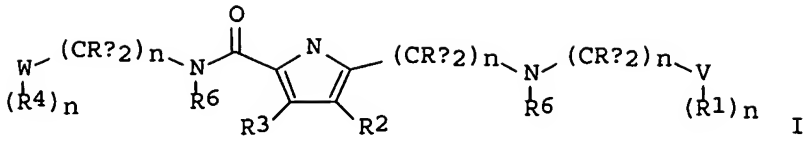

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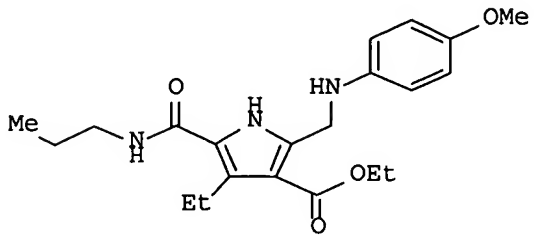


II

AB Title compds. I [wherein V = (cyclo)alkyl, aryl, heterocyclyl, or CO; W = a bond, cycloalkyl, aryl, or heterocyclyl; Ra and Rb = independently H, OR7, or (un)substituted alkyl, aryl, or heterocyclyl; R1 = independently H, halo, OR7, COR7, CO2R7, CON(R7)2, N(R7)2, SO2N(R5)2, or (un)substituted (cyclo)alkyl, aryl, or heterocyclyl; R2 = CO2R7, (CRb2)N(R7)2, (CRb2)nOR7, CON(R7)2, CONR7OR7, CONH(CRb2)qR7, CONR7NHCOR7, CONR7SO2OR7, CONH(CRb2)qCON(R7)2, or (un)substituted alkyl or aryl; R3 = H or (un)substituted alkyl, aralkyl, aryl, or heterocyclyl(alkyl); R4 = H, halo, OR7, COR7, CO2R7, CON(R7)2, N(R7)2, SO2N(R5)2, or (un)substituted (cyclo)alkyl, aryl, or heterocyclyl; R5 = independently H, or (un)substituted alkyl, aryl, or heterocyclyl; R6 = independently H, OR7, or (un)substituted alkyl, aralkyl, aryl, or heterocyclyl(alkyl); R7 = independently H or (un)substituted alkyl, aralkyl, aryl, or heterocyclyl(alkyl); n = independently 0-6; q = 0-5; or pharmaceutically acceptable salts or stereoisomers thereof] were prepared for inhibiting, modulating, and/or regulating signal transduction of both receptor type and non-receptor type tyrosine kinases. For example, N-[[5-(tert-butoxycarbonyl)-3-(ethoxycarbonyl)-4-ethyl-1H-pyrrol-2- yl]methyl]-4-methoxybenzenaminium trifluoroacetate was converted to the acid using TFA (no data), and the product amidated with propylamine to give II•TFA. Compds. of the invention inhibited insulin-like growth factor I (IGF-1R) or insulin receptor (IR) kinase activity with IC50 ≤ 100 μM. Thus, I are useful for the treatment of protein kinase related disorders, such as cancer, diabetes, autoimmune disorders, hyperproliferation disorders, aging, acromegaly, and Crohn's disease (no data).

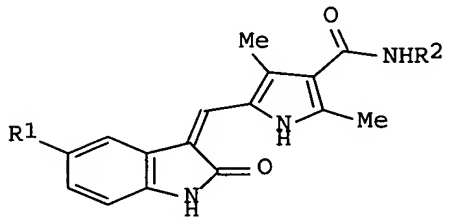
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 2 OF 31 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2004038586 EMBASE Full-text
TITLE: ZD-6474 AstraZeneca.
AUTHOR: Bates D.
CORPORATE SOURCE: D. Bates, Department of Physiology, Preclinical Veterinary School, University of Bristol, Southwell Street, Bristol BS2 8EJ, United Kingdom. Dave.Bates@bris.ac.uk
SOURCE: Current Opinion in Investigational Drugs, (2003) Vol. 4, No. 12, pp. 1468-1472. .
Refs: 41
ISSN: 1472-4472 CODEN: CIDREE
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20 Feb 2004
Last Updated on STN: 20 Feb 2004

AB ZD-6474, one of a series of inhibitors of vascular endothelial growth factor receptor tyrosine kinase, which also has activity against the epidermal growth factor receptor tyrosine kinase, is under development by AstraZeneca for the potential treatment of solid tumors. Phase 11 trials in non-small-cell lung cancer, small-cell lung cancer and myeloma were ongoing in January 2003. .COPYRGT. Current Drugs.

L38 ANSWER 3 OF 31 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:170636 CAPLUS Full-text
DOCUMENT NUMBER: 138:337929
TITLE: Discovery of 5-[5-Fluoro-2-oxo-1,2-dihydroindol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic Acid (2-Diethylaminoethyl)amide, a Novel Tyrosine Kinase Inhibitor Targeting Vascular Endothelial and Platelet-Derived Growth Factor Receptor Tyrosine Kinase
AUTHOR(S): Sun, Li; Liang, Chris; Shirazian, Sheri; Zhou, Yong; Miller, Todd; Cui, Jean; Fukuda, Juri Y.; Chu, Ji-Yu; Nematalla, Asaad; Wang, Xueyan; Chen, Hui; Sistla, Anand; Luu, Tony C.; Tang, Flora; Wei, James; Tang, Cho
CORPORATE SOURCE: SUGEN Inc., South San Francisco, CA, 94080, USA
SOURCE: Journal of Medicinal Chemistry (2003), 46(7), 1116-1119
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 138:337929
GI



I

AB To improve the antitumor properties and optimize the pharmaceutical properties including solubility and protein binding of indolin-2-ones, a series of different basic and weakly basic pyrrolylmethylidene indolinones I [R1 = H, F, Cl, Br; R2 = Et2NCH2CH2, pyridin-4-ylmethyl, 2-(1,2,3- triazol-1-yl)ethyl, etc.] were designed and synthesized. Indolinone I [R1 = F, R2 = Et2NCH2CH2 (II)] showed the best overall profile in terms of potency for the VEGF-R2 and PDGF-Rβ tyrosine kinase at biochem. and cellular levels, solubility, protein binding, and bioavailability. II is currently in phase I clin. trials for the treatment of cancers.
REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 4 OF 31 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2003455474 EMBASE Full-text
TITLE: Reduced capillary perfusion and permeability in human tumour xenografts treated with the VEGF signalling inhibitor ZD4190: An in vivo assessment using dynamic MR imaging and macromolecular contrast media.
AUTHOR: Pradel C.; Siauve N.; Bruneteau G.; Clement O.; De Bazelaire C.; Frouin F.; Wedge S.R.; Tessier J.L.; Robert P.H.; Frija G.; Cuenod C.A.
CORPORATE SOURCE: C.A. Cuenod, Laboratoire de Recherche en Imagerie, LRI-U494, Faculte Necker, Paris, France. ca@cuenod.net

SOURCE: Magnetic Resonance Imaging, (2003) Vol. 21, No. 8, pp. 845-851. .
Refs: 38
ISSN: 0730-725X CODEN: MRIMDQ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 014 Radiology
016 Cancer
027 Biophysics, Bioengineering and Medical Instrumentation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 4 Dec 2003
Last Updated on STN: 4 Dec 2003

AB We describe the use of perfusion-permeability magnetic resonance imaging (ppMRI) to study hemodynamic parameters in human prostate tumor xenografts, following treatment with the vascular endothelial growth factor-A (VEGF) receptor tyrosine kinase inhibitor, ZD4190. Using a macromolecular contrast agent (P792), a fast MR imaging protocol and a compartmental data analysis, we were able to demonstrate a significant simultaneous reduction in tumor vascular permeability, tumor vascular volume and tumor blood flow (43%, 30% and 42%, respectively) following ZD4190 treatment (100 mg/kg orally, 24 h and 2 h prior to imaging). This study indicates that MR imaging can be used to measure multiple hemodynamic parameters in tumors, and that tumor vascular permeability, volume and flow, can change in response to acute treatment with a VEGF signaling inhibitor. .COPYRGT. 2003 Elsevier Inc. All rights reserved.

L38 ANSWER 5 OF 31 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2003080906 EMBASE Full-text
TITLE: Small-molecule inhibitors of fibroblast growth factor receptor (FGFR) tyrosine kinases (TK).
AUTHOR: Manetti F.; Botta M.
CORPORATE SOURCE: M. Botta, Dipt. Farmaco Chimico Tecnologico, Universita degli Studi di Siena, Via Aldo Moro, I-53100 Siena, Italy. botta@unisi.it
SOURCE: Current Pharmaceutical Design, (2003) Vol. 9, No. 7, pp. 567-581. .
Refs: 112
ISSN: 1381-6128 CODEN: CPDEFP
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 6 Mar 2003
Last Updated on STN: 6 Mar 2003

AB Fibroblast growth factor receptors (FGFR) are members of a family of polypeptides synthesized by a variety of cell types during the processes of embryonic development and in adult tissues. FGFR have been detected in normal and malignant cells and are involved in biological events that include mitogenic and angiogenic activity with a consequent crucial role in cell differentiation and development. To activate signal transduction pathways, FGFR are coupled to fibroblast growth factors (FGF) and heparan sulfate (HS) proteoglycans to form a biologically fundamental ternary complex. Based on these considerations, a variety of inhibitors able to block the signaling cascade through a direct interaction with FGFR have been designed and investigated for their biological properties related to antiangiogenesis and antitumor activity. The purpose of this review is to focus on synthetic chemical approaches aimed at blocking tyrosine kinase (TK) receptors, members of the FGFR family. In particular, a literature survey aimed at summarizing on the structural properties that a compound should possess to show affinity toward FGFR is presented, and structure-activity relationships (SAR) on FGFR inhibitors are delined.

L38 ANSWER 6 OF 31 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2003236199 EMBASE Full-text

TITLE: Molecular mechanism for hematogenous metastasis of gastrointestinal cancer and its clinical application for therapy.
AUTHOR: Yamaguchi A.; Goi T.; Kitajima M.
CORPORATE SOURCE: Japan
SOURCE: Japanese Journal of Gastroenterology, (1 May 2003) Vol. 100, No. 5, pp. 533-539. .
Refs: 41
ISSN: 0446-6586 CODEN: NIPAA4
COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
022 Human Genetics
030 Pharmacology
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: Japanese
ENTRY DATE: Entered STN: 26 Jun 2003
Last Updated on STN: 26 Jun 2003
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L38 ANSWER 7 OF 31 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2004007226 EMBASE Full-text
TITLE: VEGF-receptor inhibitors for anti-angiogenesis.
AUTHOR: Shibuya M.
CORPORATE SOURCE: M. Shibuya, Institute of Medical Science, University of Tokyo, 4-6-1 Shirokane-dai, Minato-ku, Tokyo 108-8639, Japan
SOURCE: Folia Pharmacologica Japonica, (2003) Vol. 122, No. 6, pp. 498-503. .
Refs: 26
ISSN: 0015-5691 CODEN: NYKZAU
COUNTRY: Japan
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: Japanese
SUMMARY LANGUAGE: English; Japanese
ENTRY DATE: Entered STN: 29 Jan 2004
Last Updated on STN: 29 Jan 2004
AB Angiogenesis is deeply involved in the progression of major diseases such as cancer, diabetes, and rheumatoid arthritis. Molecular mechanism on angiogenesis was extensively studied, and several signaling systems including VEGF (VEGF-A), angiopoietin, PDGF, and ephrin were shown to be crucial for physiological angiogenesis. Interestingly, among these factors, VEGF appears to play key roles in most of the pathological angiogenesis, and other factors are considered to have additional effects on its development depending on the situation. VEGF binds and activates two tyrosine kinase receptors, VEGFR-1 (Flt-1) and VEGFR-2 (KDR/Flk-1), and stimulates endothelial cell growth, survival, and vascular permeability. VEGF induces not only tumor angiogenesis but also blood-vessel-dependent metastasis. Based on the importance of VEGF in diseases, many companies and institutes are now trying to generate appropriate small molecules as well as proteins that strongly antagonize the VEGF-VEGFR system. Several molecules quite effective for suppression of tumorigenesis and pathological angiogenesis in animal models are under clinical trials.

L38 ANSWER 8 OF 31 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2003301396 EMBASE Full-text
TITLE: Dynamic contrast-enhanced MRI of vascular changes induced by the VEGF-signalling inhibitor ZD4190 in human tumour xenografts.
AUTHOR: Checkley D.; Tessier J.J.L.; Wedge S.R.; Dukes M.; Kendrew J.; Curry B.; Middleton B.; Waterton J.C.
CORPORATE SOURCE: J.C. Waterton, Enabling Science and Technology, AstraZeneca, Alderley Park, Macclesfield, Cheshire SK10 4TG, United Kingdom. john.waterton@astrazeneca.com
SOURCE: Magnetic Resonance Imaging, (2003) Vol. 21, No. 5, pp. 475-482. .
Refs: 32

ISSN: 0730-725X CODEN: MRIMDQ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 014 Radiology
016 Cancer
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 10 Aug 2003
Last Updated on STN: 10 Aug 2003

AB Dynamic contrast-enhanced magnetic resonance imaging (DCEMRI) was used to examine the acute effects of treatment with an inhibitor of vascular endothelial growth factor (VEGF) signaling. ZD4190 is an orally bioavailable inhibitor of VEGF receptor-2 (KDR) tyrosine kinase activity, which elicits broad-spectrum antitumour activity in preclinical models following chronic once-daily dosing. Nude mice, bearing established (0.5-1.0 mL volume) human prostate (PC-3), lung (Calu-6) and breast (MDA-MB-231) tumor xenografts, were dosed with ZD4190 (p.o.) using a 1 day (0 and 22 h) or 7 day (0, 24, 48, 72, 96, 120, 144, and 166 h) treatment regimen. DCEMRI was employed 2 h after the last dose of ZD4190, using the contrast agent gadopentetate dimeglumine. Dynamic data were fit to a compartmental model to obtain voxelwise K(trans), the transfer constant for gadopentetate into the tumor. K(trans) was averaged over the entire tumor, and a multi-threshold histogram analysis was also employed to account for tumor heterogeneity. Reductions in K(trans) reflect reductions in flow, in endothelial surface area, and/or in vascular permeability. A vascular input function was obtained for each mouse simultaneously with the tumor DCEMRI data. ZD4190 treatment produced a dose-dependent (12.5-100 mg.kg(-1) per dose) reduction in K(trans) in PC-3 prostate tumors. At 100 mg.kg(-1), the largest concentration examined, ZD4190 reduced K(trans) in PC-3 tumors by 31% following 2 doses (1 day treatment regimen; $p < 0.001$) and by 53% following 8 doses (7 day regimen; $p < 0.001$). Comparative studies in the three models using a showed similar reductions in K(trans) for the lung and breast tumors using the histogram analysis, although the statistical significance was lost when K(trans) was averaged over the entire tumor. Collectively these studies suggest that DCEMRI using gadopentetate may have potential clinically, for monitoring inhibition of VEGF signaling in solid tumors. .COPYRGT. 2003 Elsevier Inc. All rights reserved.

L38 ANSWER 9 OF 31 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2003013538 EMBASE Full-text
TITLE: Molecular therapeutics in prostate cancer.
AUTHOR: Nicholson B.; Theodorescu D.
CORPORATE SOURCE: Dr. D. Theodorescu, University of Virginia, Department of Urology, P.O. Box 800422, Charlottesville, VA 22908, United States. dt9d@virtginia.edu
SOURCE: Histology and Histopathology, (2003) Vol. 18, No. 1, pp. 275-298. .
Refs: 197
ISSN: 0213-3911 CODEN: HIHIES
COUNTRY: Spain
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
028 Urology and Nephrology
038 Adverse Reactions Titles
037 Drug Literature Index
017 Public Health, Social Medicine and Epidemiology
014 Radiology
030 Pharmacology
022 Human Genetics
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 29 Jan 2003
Last Updated on STN: 29 Jan 2003

AB The purpose of this review is to provide information on the molecular basis of prostate cancer biology and to identify some of the targets for therapy, and highlight some potential strategies for molecular treatment. Here we give a synopsis of what we have learned regarding molecular biology of cancer in general and the directions research might take in the future in order to impact prostate cancer specifically. This work is certainly not encyclopedic in nature and we apologize in advance to colleagues whose work we were no able to include. Hope lies in learning to utilize some of these molecular workings for better prevention, diagnosis, and treatment of the most common solid organ cancer in men. Prostate cancer is a formidable disease and at current rates of diagnosis

will affect one-in-six men living in the United States (Greenlee et al., 2000) Many of these men are diagnosed at an early stage of the disease and can be effectively treated by surgery or radiation. However, a significant fraction of men are diagnosed with later stage disease or progress despite early curative therapeutic attempts. Unfortunately, many of these men succumb to prostate cancer, as management options are limited and not always successful. Through an understanding of the molecular processes that occur in the development and progression of prostate cancer, novel therapies will arise that will provide longer survival, better quality of life, and a chance for cure in men afflicted with this disease.

L38 ANSWER 10 OF 31 EMBASE

ACCESSION NUMBER: 2004099464 EMBASE Full-text
TITLE: Emerging Roles of Targeted Small Molecule Protein-Tyrosine Kinase Inhibitors in Cancer Therapy.
AUTHOR: Smith J.K.; Mamoon N.M.; Duhe R.J.
CORPORATE SOURCE: R.J. Duhe, Dept. of Pharmacology and Toxicology, Univ. of Mississippi Medical Center, Jackson, MS 39216-4505, United States. RDUHE@pharmacology.umsmed.edu
SOURCE: Oncology Research, (2003) Vol. 14, No. 4-5, pp. 175-225. .
Refs: 422
ISSN: 0965-0407 CODEN: ONREE8
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 18 Mar 2004
Last Updated on STN: 18 Mar 2004

AB Targeted protein-tyrosine kinase inhibitors (PTKIs) comprise a new, rapidly evolving class of low molecular weight anticancer drugs. Two members of this class, imatinib (Gleevec®) and gefitinib (Iressa®), are currently approved for market use in the United States. This review discusses the scientific history behind these two PTKI drugs, including the role of the targeted kinase in cancer etiology, the biochemistry of selective inhibition, the evaluation of clinical efficacy, and the mechanisms whereby drug resistance has emerged. Other PTKIs undergoing clinical evaluation are also described, including epidermal growth factor receptor kinase inhibitors (erlotinib, PKI166, and CI-1033) and PTKIs designed to disrupt tumor vascularization (SU5416, SU6668, SU11248, PTK787, and ZD6474). How might one apply current knowledge to the efficient development of new agents that would target as-yet-unexploited oncogenic PTKs such as chimeric anaplastic leukemia kinases or Janus kinases? Ideally, the targets should contain structurally distinct drug interaction epitopes, although it is not necessary that these epitopes be unique to a single target, because effective drugs may inhibit multiple kinases involved in an oncogenic process. Oral availability is a highly desirable feature because daily oral administration can maintain a sustained efficacious plasma concentration, whereas intermittent parenteral administration may not. Perhaps most importantly, one must verify the presence of an appropriate molecular target on a case-by-case basis before selecting a patient for PTKI therapy. Thus, the development of molecularly targeted diagnostic tools will be crucial to the ultimate success of molecularly targeted PTKI therapy.

L38 ANSWER 11 OF 31 EMBASE

ACCESSION NUMBER: 2003080914 EMBASE Full-text
TITLE: Vascular Endothelial Cell Growth Factor (VEGF), an emerging target for cancer chemotherapy.
AUTHOR: Shinkaruk S.; Bayle M.; Lain G.; Deleris G.
CORPORATE SOURCE: G. Deleris, INSERM U443, Bio-Organic Chemical Group, University Victor Segalen Bordeaux 2, F33076 Bordeaux Cedex, France. gerard.deleris@u-bordeaux2.fr
SOURCE: Current Medicinal Chemistry - Anti-Cancer Agents, (2003) Vol. 3, No. 2, pp. 95-117. .
Refs: 195
ISSN: 1568-0118 CODEN: CMCACI
COUNTRY: Netherlands

DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 6 Mar 2003
Last Updated on STN: 6 Mar 2003

AB Angiogenesis is a process of development and of growth of new capillary blood vessels from pre-existing vessels. When pathological, it contributes to the development of numerous types of tumors, and the formation of metastases. In order to grow, carcinoma need new blood vessels to form so that they can feed themselves. Therefore, nowadays the concept according to which the development of cancer is angiogenesis dependant is generally recognized. This concept makes the control of tumoral angiogenesis one of the promising therapeutic ways in cancerology. The transition from the latent phase to the invasive and metastatic phase of a cancer is linked to what is called the angiogenic switch. It implies complex cellular and molecular interactions between cancerous cells, endothelial cells and the components of the extra-cellular matrix and namely the existence of specific proteins secreted by the tumoral cells able to stimulate the proliferation of capillary endothelial cells. Among them, VEGF, Vascular Endothelial Growth Factor was found in several types of tumors. It has shown a tumoral angiogenic activity in vitro and in vivo, and thus is a privileged target for the control of angiogenesis in an anti-tumoral goal. The role of VEGF in tumoral angiogenesis has been extensively studied. It has been proved to undergo as well autocrine as paracrine stimulation of tumoral angiogenesis. During the last few years, several members of the VEGF family have been described namely the VEGF-A, B, C, D, E and placenta growth factor (PlGF) among which VEGF-A (121 aminoacids) plays a role of prime importance in angiogenesis. VEGF is a 45 kDA glycoprotein, homodimeric, basic, and able to bind heparin. The three-dimensional structure of VEGF has been recently determined, by X-rays diffraction, and NMR spectroscopy. The different forms of the VEGF bind to receptors that exhibit a tyrosine-kinase activity (RTK). The specific action of the VEGF on the endothelial cells is mainly regulated by two types of RTK of the VEGF family, VEGFR1, or Flt-1, and VEGFR2, or KDR/Flk-1. Mutagenesis studies have shown that only a small number of VEGF residues are important and essential for the binding with RTK. Data described to date from the studies of VEGF/RTK interactios agree to the hypothesis that KDR receptor is the main human receptor responsible for the VEGF activity in both physiological and pathological vascular development, and VEGF-KDR signalling pathway has been validated as a priority target for the development of anti- and pro-angiogenic agents. Therefore angiogenesis mediated by VEGF constitutes a new target for anti-cancer therapy which has explored through different ways of intervention aiming at the blocking of the tumoral angiogenesis. The main ones are: -Struggle against the stroma degradation and invasion by the neo-vessels -Inhibition of activated endothelial cells. -Inhibition of angiogenic factors production and of their receptors. -Inhibition of the VEGF signal pathway, by peptides blocking the bond between VEGF and its receptors through the inhibition of intracellular transduction of VEGF signal. In conclusion, this bibliographic study allows to situate works of medicinal chemistry in the context of present knowledge concerning the vascular endothelial growth factor (VEGF) and its role in angiogenesis.

L38 ANSWER 12 OF 31 EMBASE
ACCESSION NUMBER: 2004497595 EMBASE Full-text
TITLE: Measuring tumour vascular response to antivascular and antiangiogenic drugs.
AUTHOR: Tozer G.M.
CORPORATE SOURCE: Dr. G.M. Tozer, Tumour Microcirculation Group, Gray Cancer Institute, Mount Vernon Hospital, PO Box 100, Northwood, Middlesex HA6 2JR, United Kingdom
SOURCE: British Journal of Radiology, (2003) Vol. 76, No. SPEC. ISS. 1, pp. S23-S35. .
Refs: 93
ISSN: 0007-1285 CODEN: BJRAAP
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
023 Nuclear Medicine
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index

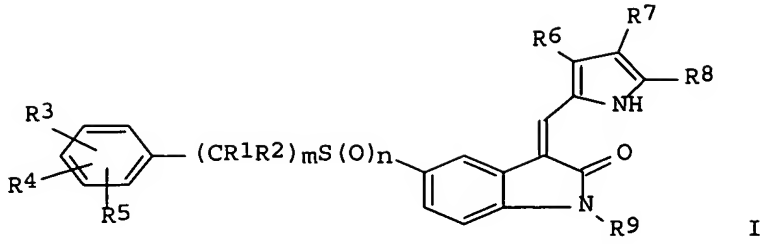
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 9 Dec 2004
Last Updated on STN: 9 Dec 2004

AB The tumour vasculature is an attractive target for therapy because of its accessibility to blood-borne anticancer agents and the reliance of most tumour cells on an intact vascular supply for their survival. For convenience, therapeutic targeting of the tumour vasculature can be divided into antiangiogenic approaches, which target the process of new blood vessel development and antivascular approaches, which target the established tumour vasculature. Many agents are now in clinical trial for the treatment of cancer by these methods. The main aim of this article is to describe the vascular effects of some of these agents and identify suitable end-points for measuring efficacy in early clinical trials. For drugs which are active below their maximum tolerated dose (MTD), measurement of vascular end-points is required to determine the most effective dosing/scheduling protocols. In addition, many of the current and developing antiangiogenic agents have additional mechanisms of action unrelated to angiogenesis per se, requiring measurement of vascular end-points to understand their mechanisms of action. Measurement of tumour microvascular density (MVD) from tumour biopsies is a common method for assessing the efficacy of antiangiogenic drugs. The limitations of this method and alternative end-points, which take into account vascular function, are discussed. Pre-clinical data regarding tumour response to the antivascular agent combretastatin A-4 3-O-phosphate (CA-4-P) are discussed in the context of guiding clinical trial planning. Finally, the accessibility of vascular end-points for clinical imaging is addressed. .COPYRGT. 2003 The British Institute of Radiology.

L38 ANSWER 13 OF 31 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:927188 CAPLUS Full-text
DOCUMENT NUMBER: 138:14005
TITLE: Preparation of 5-aralkylsulfonyl-3-(pyrrol-2-ylmethylidene)-2-indolinone derivatives as kinase inhibitors
INVENTOR(S): Cui, Jingrong; Ramphal, Yudhi; Liang, Congxin; Sun, Li; Wei, Chung Chen; Tang, Peng Cho
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 479 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002096361	A2	20021205	WO 2002-US16841	20020530
WO 2002096361	A3	20030313		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003125370	A1	20030703	US 2002-157007	20020530
US 6599902	B2	20030729		
PRIORITY APPLN. INFO.:			US 2001-294544P P	20010530
			US 2001-328408P P	20011010

OTHER SOURCE(S): MARPAT 138:14005
GI



I

AB The present invention relates to certain 5-aralkylsulfonyl-3-(pyrrol-2- ylmethylidene)-2-indolinone derivs. (shown as I; see below for variable definitions; e.g. 2,4-dimethyl-5-(2-oxo-5-phenylmethanesulfonyl-1,2- dihydroindol-(3Z)-ylidenemethyl)-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide) that inhibit kinases (no data), in particular met kinase. Pharmaceutical compns. comprising these compds., methods of treating diseases mediated by kinases using pharmaceutical compns. comprising these compds., and methods of preparing them are also disclosed. In I: n = 0-2; m = 1-3; R1 and R2 = H or alkyl; R3, R4, and R5 = H, halo, alkyl, cycloalkyl, haloalkyl, hydroxy, alkoxy, alkoxycarbonyl, haloalkoxy, cyano, carboxy, carboxyalkyl, nitro, aryl, aryloxy, heteroaryl, heteroaryloxy, -(alkylene)-CONR10R11, -CONR10R11, or - NR10R11 (R10 is H or alkyl, and R11 is aryl, heteroaryl, heterocycle, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, acetylalkyl, cyanoalkyl, carboxyalkyl, alkoxycarbonylalkyl, heteroaralkyl, aralkyl, or heterocyclylalkyl wherein the alkyl chain in aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, aralkyl, heteroaralkyl, or heterocyclylalkyl is optionally substituted with one or two hydroxy, or R10 and R11 together with the N atom to which they are attached combine to form saturated or unsatd. heterocycloamino). R6 is H, alkyl, cycloalkyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl, heterocyclylalkyl, aryl, heteroaryl, carboxy, alkoxycarbonyl, heterocyclylcarbonyl, aminoalkylcarbonyl, alkylaminoalkylcarbonyl, dialkylaminoalkylcarbonyl, -CONR10R11 or -(alkylene)-CONR10R11. R7 and R8 = H, alkyl, cycloalkyl, heterocyclylalkyl, -COR12, -(alkylene)-COR12 (R12 = alkoxy, hydroxy, or heterocycle, alkylamino, dialkylamino), -SO2R14, -CONR13R14, or -(alkylene)-CONR13R14 (R13 is H or alkyl, and R14 is aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, hydroxyalkyl, acetylalkyl, cyanoalkyl, carboxyalkyl, alkoxycarbonylalkyl, heteroaralkyl, or heterocyclylalkyl wherein the alkyl chain in aminoalkyl, heteroaralkyl, heteroaralkyl, or heterocyclylalkyl is optionally substituted with one or two hydroxy group(s), or when R13 and R14 are attached to a N atom R13 and R14 together with the N atom to which they are attached form saturated or unsatd. heterocycloamino). R6 and R7 or R7 and R8 can combine to form a saturated or unsatd. 5 to 8 membered ring; and R9 is: H or alkyl; -PO(OR15)2 where each R15 = H or alkyl; -COR16 where R16 is H or alkyl; or -CHR17NR18R19 where R17 is H or alkyl, and R18 and R19 = H or alkyl or R18 and R19 together with the N atom to which they are attached form heterocycloamino. Although the methods of preparation are not claimed, 375 example prepns. of I plus addnl. prepns. of intermediates are included.

L38 ANSWER 14 OF 31 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:172092 CAPLUS Full-text
DOCUMENT NUMBER: 136:211879
TITLE: Identification of constitutively-activated receptors and ion channels for identification of antagonists and endogenous ligands
INVENTOR(S): Beachy, Philip A.; Taipale, Jussi
PATENT ASSIGNEE(S): Johns Hopkins University School of Medicine, USA
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002018590	A2	20020307	WO 2001-US27088	20010830
WO 2002018590	A3	20030227		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,
HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO,
RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ,
VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2001086945	A5	20020313	AU 2001-86945		20010830
US 2002157119	A1	20021024	US 2001-943641		20010830
PRIORITY APPLN. INFO.:			US 2000-229243P	P	20000830
			WO 2001-US27088	W	20010830

AB The present invention related to methods and reagents for generating and using activating mutations of receptors and ion channels. The method involves screening a library of variants, e.g. created by in vitro mutagenesis, for constitutive activity. This can be done by screening for levels of a second messenger, e.g. by induction of a second messenger-dependent reporter gene. The host cell may be manipulated to increase the sensitivity of the response of the reporter process to the induction. The method allows the identification of receptors and their adverse effects and of inhibitors without the need to know their endogenous ligand or function.

L38 ANSWER 15 OF 31 EMBASE

ACCESSION NUMBER: 2002206850 EMBASE Full-text
TITLE: Kinase insert domain-containing receptor kinase inhibitors as anti-angiogenic agents.
AUTHOR: Bilodeau M.T.; Fraley M.E.; Hartman G.D.
CORPORATE SOURCE: G.D. Hartman, Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA 19486, United States
SOURCE: Expert Opinion on Investigational Drugs, (2002) Vol. 11, No. 6, pp. 737-745. .
Refs: 68
ISSN: 1354-3784 CODEN: EOIDER
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 27 Jun 2002
Last Updated on STN: 27 Jun 2002

AB A variety of data accumulated during the past 10 years indicates that vascular endothelial growth factor-mediated angiogenesis is a key process in the growth of solid tumours. Efficacious and specific modulation of that signalling event through the inhibition of the cognate tyrosine kinase kinase insert domain-containing receptor (Flk-1) has been reported. A variety of small molecule kinase-domain-containing receptor kinase inhibitors, including SU-5416, SU-6668, PTK-787, midostaurin, ZD4190 and ZD6474, have progressed to the clinical testing stage and this has allowed the direct and critical inspection of preclinical and clinical behaviour. The variety of potency, kinase selectivity and pharmacokinetic profiles offered by this group of compounds is providing important guidance for the efficacious use of these agents today and the design of second and third generation compounds for the future.

L38 ANSWER 16 OF 31 EMBASE

ACCESSION NUMBER: 2002342730 EMBASE Full-text
TITLE: The role of signal transduction in cancer treatment and drug resistance.
AUTHOR: Liem A.A.; Chamberlain M.P.; Wolf C.R.; Thompson A.M.
CORPORATE SOURCE: A.M. Thompson, Dept. of Surgery/Molecular Oncology, Ninewells Hospital, University of Dundee, Dundee DD1 9SY, United Kingdom. a.m.thompson@dundee.ac.uk
SOURCE: European Journal of Surgical Oncology, (2002) Vol. 28, No. 6, pp. 679-684. .
Refs: 81
ISSN: 0748-7983 CODEN: EJSOE7

COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 17 Oct 2002
Last Updated on STN: 17 Oct 2002

AB Drug resistance in the treatment of cancer still remains a major clinical challenge, in part due to an insufficient understanding of the pathways by which these drugs interact with the mechanisms underlying cellular behaviour and cancer pathogenesis. Signal transduction involves cell differentiation, proliferation and cell death with alterations in these mechanisms being involved in the pathogenesis of cancer. It has been postulated that such pathways could be linked to anti-cancer drug resistance. Recently, novel approaches to overcome anti-cancer drug resistance through manipulation of signal transduction pathways, have been introduced in clinical trials. In this article we present a review of the current understanding in the field of signal transduction and the existing evidence for its role in drug resistance. We also discuss its clinical relevance with regard to overcoming drug resistance. .COPYRGT. 2002 Elsevier Science Ltd. All rights reserved.

L38 ANSWER 17 OF 31 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2002431512 EMBASE Full-text
TITLE: Vascular endothelial growth factor as a target opportunity in hematological malignancies.
AUTHOR: Bellamy W.T.
CORPORATE SOURCE: Dr. W.T. Bellamy, Department of Pathology, University of Arizona, 1501 North Campbell Avenue, Tucson, AZ 85724, United States. wbellamy@u.arizona.edu
SOURCE: Current Opinion in Oncology, (2002) Vol. 14, No. 6, pp. 649-656. .
Refs: 81
ISSN: 1040-8746 CODEN: CUOOE8
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
025 Hematology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 12 Dec 2002
Last Updated on STN: 12 Dec 2002

AB Vascular endothelial growth factor (VEGF) is a potent angiogenic peptide with diverse biologic effects. There are seven members of the VEGF family, VEGF-A through VEGF-E, placental growth factor and the newly described, tissue-specific endocrine gland-derived VEGF. VEGF expression is induced by a number of stimuli including hypoxia, activated oncogenes, and inflammatory cytokines while negative regulators include wild type von Hippel-Lindau and p53 tumor suppressor genes. VEGF activity is mediated through interactions with high affinity tyrosine kinase receptors. To date, three have been identified. Interaction with these receptors activates multiple signal pathways leading to the diverse biologic activity of VEGF. Evidence suggests that VEGF is also a survival factor for endothelial cells and perhaps tumor cells. The importance of angiogenic factors such as VEGF, while clearly established in solid tumors, has not been fully elucidated in human hematopoietic neoplasms. Evolving data generally that elevated levels of VEGF confer a poor prognosis to patients with these diseases. The central role of VEGF in angiogenesis coupled with the relatively restricted expression of its receptors, has led to the development of a number of agents to target this system that are currently under clinical investigation. .COPYRGT. 2002 Lippincott Williams & Wilkins, Inc.

L38 ANSWER 18 OF 31 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2002419526 EMBASE Full-text
TITLE: Role of vascular endothelial growth factor during breast cancer.
AUTHOR: Kushlinskii N.E.; Gershtein E.S.

CORPORATE SOURCE: N.E. Kushlinskii, Laboratory of Clinical Biochemistry, N. N. Blokhin Russian Oncology Ctr., Russian Academy of Medical Sciences, Moscow, Russian Federation
SOURCE: Bulletin of Experimental Biology and Medicine, (1 Jun 2002) Vol. 133, No. 6, pp. 521-528. .
Refs: 86
ISSN: 0007-4888 CODEN: BEXBAN
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
003 Endocrinology
038 Adverse Reactions Titles
037 Drug Literature Index
005 General Pathology and Pathological Anatomy
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 5 Dec 2002
Last Updated on STN: 5 Dec 2002

AB We review the results of experimental and clinical observations on neoangiogenesis in patients with breast cancer. Vascular endothelial growth factor is an important positive regulator of this process. Experiments showed the possibility of using various direct and indirect antiangiogenic means in the therapy of breast cancer, but clinical efficiency of these methods was not proved. Expression of vascular endothelial growth factor can serve as a prognostic criterion in breast cancer. Antiangiogenic preparations should not be used as monotherapy, but as the treatment complementary to standard therapy.

L38 ANSWER 19 OF 31 EMBASE
ACCESSION NUMBER: 2002211728 EMBASE Full-text
TITLE: [Angiogenesis inhibitors: A new therapeutic approach in cancer therapy].
ANGIOGENESE-INHIBITOREN: EINE NEUE WIRKSTOFFGRUPPE IN DER KREBSTHERAPIE.
AUTHOR: Ibrom W.
CORPORATE SOURCE: Dr. W. Ibrom, Apotheke des Krankhs. St. Josef GmbH, Ringstr. 60A, A-5280 Braunau am Inn, Austria. wolfgang.ibrom@khbr.or.at
SOURCE: Krankenhauspharmazie, (2002) Vol. 23, No. 5, pp. 181-192. .
Refs: 40
ISSN: 0173-7597 CODEN: KRANDZ
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: German
SUMMARY LANGUAGE: English; German
ENTRY DATE: Entered STN: 27 Jun 2002
Last Updated on STN: 27 Jun 2002

AB The growth of solid tumors and metastases beyond a limited size of 1-2 mm(3) in diameter depends on angiogenesis. This dynamic process is tightly controlled by a large number of proangiogenic and antiangiogenic factors, their receptors and signal transduction pathways respectively which are representing new targets for an antiangiogenic therapy. Many of these factors are involved with an intrinsic or associated tyrosine kinase activity. The pharmacodynamic targeting of tumor angiogenesis may be divided into seven major categories: 1. Antagonists of angiogenic growth factors 2. Inhibitors of endothelial cell signal transduction 3. Inhibitors of endothelial cell proliferation and migration 4. Inhibitors of cell adhesion molecules 5. Vascular thrombosis inducing agents 6. Non-selective angiogenesis inhibitors 6.1 Matrix metalloproteinase inhibitors 6.2 Inhibitors of cofactors 7. Anti-angiogenic agents with different mechanisms of action Angiogenesis inhibitors were investigated in clinical trials for the therapy of solid tumors, like lung (SCLC, NSCLC), breast, colon, gastric tumors, glioblastoma, melanoma, in addition lymphomas and multiple myeloma, where effective conventional therapies and regimes do not exist so far. Finally the antiangiogenic therapy is compared with conventional chemotherapy. The pharmacological profile of angiogenesis inhibition differs basically from established chemotherapy: As a result of in the unique therapeutic target at the

tumor endothelial cells, the drug resistance may be less a problem. Other differerences are the moderate spectrum of side effects, the longterm maintenance therapy and the cytostatic mechanism of action. Also combination of antiangiogenic agents with conventional cytotoxic drugs enhances the effect of the latter. At the end of 2001 approx. 50 angiogenesis inhibitors were investigated in clinical studies I-III, in the next three years the first antiangiogenic drug for the treatment of neoplasms will be on approval.

L38 ANSWER 20 OF 31 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2002281463 EMBASE Full-text
TITLE: [Effects of the administration of antipsychotic drugs on the regional brain expression of immediate early genes (IEGs)].
EFFETTI DELLA SOMMINISTRAZIONE DI ANTIPSICOTICI SULL'ESPRESSIONE REGIONALE CEREBRALE DI GENI IMMEDIATI PRECOCI (IEG).
AUTHOR: Kotzalidis G.D.; Facchi A.; Tarsitani L.; Pancheri P.
CORPORATE SOURCE: Dr. G.D. Kotzalidis, III Clinica Psichiatrica, Universita di Roma La Sapienza, Viale dell'Universita 30, 00185 Roma, Italy
SOURCE: Giornale Italiano di Psicopatologia, (2002) Vol. 8, No. 2, pp. 171-220. .
Refs: 423
ISSN: 1592-1107 CODEN: GIPIAJ
COUNTRY: Italy
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 030 Pharmacology
032 Psychiatry
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: Italian
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 22 Aug 2002
Last Updated on STN: 22 Aug 2002

AB Antipsychotics were found to induce immediate early genes (IEGs) in selected brain regions. There is a net splitting between the effects of classical neuroleptics and the newer antipsychotics in their effects on IEG expression, in that the former induce them in the most motor portion of the striatum, whereas the latter are less potent in this area. Almost all antipsychotics induce IEGs in the nucleus accumbens septi, with a difference accumbens minus striatum which is greater for atypical antipsychotics. Standard areas of IEG measurement after antipsychotics include the striatum, both its dorsolateral (motor) and ventromedial (limbic or «emotional») portions, the nucleus accumbens and the major island of Calleja, and the medial prefrontal cortex, whereas other important areas, such as the amygdala, the thalamus, the hippocampus, and the lateral septum are less investigated. Atypical antipsychotics tend to induce IEGs in the prefrontal cortex whereas classical neuroleptics tend to be inactive at this respect. The most frequently investigated IEG is c-fos, but c-jun or other Fos and Jun proteins were also extensively investigated, but not for all antipsychotics. These IEGs are acutely, but transiently induced by these drugs; less investigations were carried-out on the induction of more persistent forms of oncogenes and their results are usually at odds with what was found for acute IEG induction, specially for the older neuroleptics, which tend to be more similar to the atypicals at this regard. IEG induction pattern and antipsychotic or extrapyramidal side effect induction profile usually correlate, with some notable exception. Discrepancies between IEG induction and antipsychotic potential should induce to evaluate new drugs with other experimental paradigms as well, to avoid that potentially useful drugs are rejected only on the grounds that they do not induce IEGs as desired. Most drugs were investigated in only a few studies, with most studies testing the effects of major class representatives, such as haloperidol, clozapine, and sulpiride, and entire classes, such as thioxanthenes, lacking from the list. Regarding the mechanisms of IEG induction, D(2) blockade appears to be one the most important mechanisms in most areas, but other mechanisms may participate as well. 5-HT(2A) blockade, which is a mechanism commonly advocated for atypical antipsychotic action, should actually bring about a reduction in c-fos expression, therefore, it should not be considered as being directly responsible for c-fos induction. D(3) mechanisms should not be important for the action of atypicals on c-fos. Indirect mechanisms could involve NMDA activation. Other, transiently expressed genes, such as those involved in the wingless pathway, despite their reported involvement in schizophrenia, have not been investigated as related to antipsychotics. IEG expression is an adequate and useful test to predict antipsychotic

action and/or extrapyramidal side effect induction only if its results are combined with those of other screening tests and its results should not be considered as a constraint.

L38 ANSWER 21 OF 31 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2002104676 EMBASE Full-text
TITLE: CGP 79787D (PTK787/ZK222584), CGP 84738, NVP-AAC789, NVP-AAD777 and related 1-anilino-(4-pyridylmethyl)phthalazines as inhibitors of VEGF- and bFGF-induced angiogenesis.
AUTHOR: Bold G.; Frei J.; Furet P.; Manley P.W.; Bruggen J.; Cozens R.; Ferrari S.; Hofmann F.; Martiny-Baron G.; Mestan J.; Meyer T.; Wood J.M.
CORPORATE SOURCE: G. Bold, Novartis Pharma AG, CH-4057 Basel, Switzerland
SOURCE: Drugs of the Future, (2002) Vol. 27, No. 1, pp. 43-55. .
Refs: 67
ISSN: 0377-8282 CODEN: DRFUD4
COUNTRY: Spain
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 4 Apr 2002
Last Updated on STN: 4 Apr 2002

AB 1-Anilino-(4-pyridylmethyl)phthalazines are potent, selective and orally well absorbed inhibitors of vascular endothelial growth factor (VEGF) receptor tyrosine kinases. In vitro they block VEGF-stimulated autophosphorylation of KDR expressing cells, leading to the inhibition of survival effects of VEGF on endothelial cells. They also block PDGF-mediated effects at slightly higher concentrations but do not affect other pathways such as the bFGF receptor. To prove their efficacy in vivo, the effects of 1-anilino-(4-pyridylmethyl)phthalazines on cytokine-induced angiogenic responses were studied in a growth factor implant model in normal mice. In sharp contrast to their in vitro profile, in vivo 1-anilino-(4-pyridylmethyl)-phthalazines do not only inhibit VEGF signaling but in some cases they also interfere with the bFGF-induced angiogenesis pathway. In studies with tumor models expressing VEGF and BFGF in different ratios, it was demonstrated that inhibition of both VEGF- and BFGF-induced neovascularization increases the spectrum of antitumor efficacy. In regard to tolerability, no differences were observed. Inhibition of tumor growth was accompanied by profound effects on tumor vascularization and also reduction in vascular permeability. In a collaboration between Schering AG and Novartis, PTK787, a representative of the structural class of 1-anilino-(4-pyridyl-methyl)phthalazines, is currently in clinical trials in cancer patients (53). Exciting results with PTK787 in other areas indicate that these compounds provide a novel therapeutic approach, not only for the treatment of cancer but also for the treatment of other diseases characterized by aberrant vascular permeability and neovascularization.

L38 ANSWER 22 OF 31 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2002349994 EMBASE Full-text
TITLE: The angiogenic switch in solid tumors: Clinical implications.
AUTHOR: Tosetti F.; Benelli R.; Albini A.
CORPORATE SOURCE: F. Tosetti, Laboratory of Molecular Biology, National Cancer Research Institute, Genoa, Italy
SOURCE: Tumori, (2002) Vol. 1, No. 6 SUPPL., pp. S9-S11. .
Refs: 20
ISSN: 0300-8916 CODEN: TUMOAB
COUNTRY: Italy
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
ENTRY DATE: Entered STN: 17 Oct 2002
Last Updated on STN: 17 Oct 2002

DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

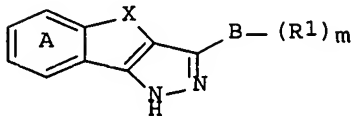
L38 ANSWER 23 OF 31 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:851123 CAPLUS Full-text
DOCUMENT NUMBER: 136:5985
TITLE: Preparation of tricyclic pyrazole derivatives as tyrosine kinase inhibitors for treatment of angiogenesis-related diseases
INVENTOR(S): Doyle, Kevin J.; Rafferty, Paul; Steele, Robert W.; Wilkins, David J.; Arnold, Lee D.; Hockley, Michael; Ericsson, Anna M.; Iwasaki, Nobuhiko; Ogawa, Nobuo
PATENT ASSIGNEE(S): Knoll G.m.b.H., Germany
SOURCE: PCT Int. Appl., 183 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001087846	A2	20011122	WO 2001-US16153	20010517
WO 2001087846	A3	20020321		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6462036	B1	20021008	US 2000-573366	20000517
CA 2409225	AA	20011122	CA 2001-2409225	20010517
EP 1289525	A2	20030312	EP 2001-937553	20010517
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003533514	T2	20031111	JP 2001-584242	20010517

PRIORITY APPLN. INFO.:	US 2000-573366	A1	20000517
	US 1998-107467P	P	19981106
	WO 1999-US26105	A2	19991104
	WO 2001-US16153	W	20010517

OTHER SOURCE(S): MARPAT 136:5985
GI



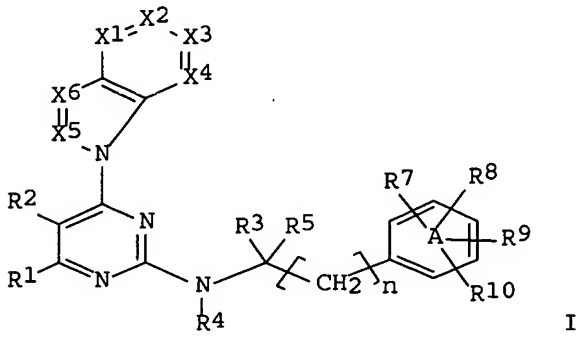
I

AB Title compds. I [m = 1-10; X = (CH2)n, CO, O, C:NOR10, NR11, (CH2)n, S, SO, or SO2; n = 1-3; R10 = alkyl; R11 = (un)substituted alkyl or Ph; B = (cyclo)alkyl, aryl, pyridyl, thienyl, furyl, or pyrrolyl; R1 = H, halo, OH, NO2, CN, hydroxyamidino, CH2NH2, formamidomethyl, (un)substituted alkenyl(oxy), alkynyl, or YW; Y = absent or alkyl, alkoxy, O, S, or CO; W = H, OH, (un)substituted Ph, alkoxy, or amino; ring A is optionally substituted with halo, OH, NO2, CN, or (un)substituted alkyl, alkoxy, PhO, carboxy, carbamoyl, amino, amido, aralkyl, alkenyl, or alkynyl; with provisos; and racemic mixts., racemic diastereomeric mixts., tautomers, optical isomers, and pharmaceutically acceptable salts thereof] were prepared as protein kinase inhibitors, especially tyrosine kinase inhibitors. Thus, indan-1-one hydrazone (preparation given) in THF at 0° was treated with BuLi and then with Me 3,4,5-trimethoxybenzoate to give 3-(3,4,5-trimethoxyphenyl)-1,4-dihydroindeno[1,2-c]pyrazole. Example compds. significantly inhibited KDR kinase at concns. of ≤ 50 μM.

L38 ANSWER 24 OF 31 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:12273 CAPLUS Full-text
DOCUMENT NUMBER: 134:86271
TITLE: Preparation of pyrimidine derivatives as Src-family protein tyrosine kinase inhibitor compounds
INVENTOR(S): Armstrong, Helen M.; Beresis, Richard; Goulet, Joung L.; Holmes, Mark A.; Hong, Xingfang; Mills, Sander G.; Parsons, William H.; Sinclair, Peter J.; Steiner, Mark G.; Wong, Frederick; Zaller, Dennis M.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 470 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001000213	A1	20010104	WO 2000-US17443	20000626
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2383546	AA	20010104	CA 2000-2383546	20000626
EP 1206265	A1	20020522	EP 2000-941701	20000626
EP 1206265	B1	20031112		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
US 6498165	B1	20021224	US 2000-604305	20000626
JP 2003523942	T2	20030812	JP 2001-505922	20000626
AT 253915	E	20031115	AT 2000-941701	20000626
PRIORITY APPLN. INFO.:			US 1999-141639P P	19990630
			WO 2000-US17443 W	20000626

OTHER SOURCE(S): MARPAT 134:86271
GI



I

AB What are claimed are pyrimidine compds. (shown as I), or their pharmaceutically acceptable salts, hydrates, solvates, crystal forms and individual diastereomers, and pharmaceutical compns. including the same and their use as inhibitors of tyrosine kinase enzymes and consequently their use in the prophylaxis and treatment of protein tyrosine kinase-associated disorders, such as immune diseases, hyperproliferative disorders and other diseases in which inappropriate protein kinase action is believed to play a role, such as cancer, angiogenesis, atherosclerosis, graft rejection, rheumatoid arthritis and

psoriasis. In I, R1, R2 = independently H, halo, OH, SH, CN, NO2, alkyl, alkoxy, acyloxy, alkoxycarbonyloxy, carbamoyloxy, alkylthio, sulfinyl, sulfonyl, acyl, alkoxycarbonyl, carbamoyl, amino, acylamino, ureido, sulfamoyl, sulfonylamino, or R1 and R2 can join together to form a fused methylenedioxy ring or a fused 6-membered aromatic ring; terms such as 'alkyl' here and below are further defined in the claims. R3, R5 = independently H, C1-C6-alkyl unsubstituted or substituted with 1-3 substituents, aryl, or R3 and R5 taken together can represent :O; R3 or R5 can represent a 2 or 3 C methylene bridge forming a ring of 5-8 atoms fused to the A ring. R4 = H, C1-C6-alkyl, C1-C6-alkoxyl. X1, X2, X3, X4 in -X1:X2-X3:X4- are substituted or unsubstituted CH or N where 0-2 of X1, X2, X3, X4 are N. X5, X6 = independently N, C, optionally substituted CH. A ring = Ph, naphthyl, pyridyl, pyrazinyl, pyrimidinyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, benzothienyl, benzofuranyl, indolyl, imidazolyl, benzimidazolyl, thiadiazolyl. R7, R8, R9, R10 = independently H, halo, OH, SH, CN, NO2, N3, N2+BF4-, alkyl, alkoxy, alkylthio, sulfinyl, sulfonyl, C1-C6-alkyl, C1-C6-perfluoroalkyl, acyl, alkoxycarbonyl, carbamoyl, acyloxy, alkoxycarbonyloxy, carbamoyloxy, amino, acylamino, ureido, sulfamoyl, sulfonylamino, two of R7, R8, R9, and R10 when on adjacent carbons join together to form a methylenedioxy bridge. N = 0-2. More than 500 example prepns. are given, but no preparative method is claimed and no data relating to the usefulness of the compds. are given.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 25 OF 31 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2001333997 EMBASE Full-text
TITLE: Tumor angiogenesis as a therapeutic target.
AUTHOR: Matter A.
CORPORATE SOURCE: A. Matter, Oncology Research, Novartis Pharma AG, 4002 Basel, Switzerland. alex.matter@pharma.novartis.com
SOURCE: Drug Discovery Today, (1 Oct 2001) Vol. 6, No. 19, pp. 1005-1024. .
Refs: 208
ISSN: 1359-6446 CODEN: DDTOFS
PUBLISHER IDENT.: S 1359-6446(01)01939-0
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 11 Oct 2001
Last Updated on STN: 11 Oct 2001

AB Angiogenesis - the formation of new blood vessels within a tumor (or many other tissue types) - has become a hotbed of pharmacological research as well as industrial drug discovery. This is the result of the efforts of a generation of scientists elucidating the complex (patho)physiological, biochemical and molecular events accompanying angiogenesis. It is estimated that >300 drug candidates are currently in various stages of testing, and it is, therefore, impossible to capture all of this in a brief review. Therefore, the emphasis here is on relatively advanced projects that are either in preclinical or clinical development, thus neglecting, to a large extent, the many exciting avenues being pursued in both academic and biotechnology laboratories. Although the potential of the approaches described cannot be overestimated, it is also important to note that there is still no drug on the market that achieves clinical benefit based on a selective modulation or inhibition of angiogenesis. Copyright .COPYRGT. 2001 Elsevier Science Ltd.

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ACCESSION NUMBER: 2001354830 EMBASE Full-text
TITLE: Molecular therapy for multiple myeloma.
AUTHOR: Martinelli G.; Tosi P.; Ottaviani E.; Soverini S.; Tura S.
CORPORATE SOURCE: Dr. G. Martinelli, Molecular Biology Unit, Inst. Hematol./Med. Oncol. Seragnoli, University of Bologna, via Massarenti 9, 40138 Bologna, Italy.
gmartino@kaiser.alma.unibo.it
SOURCE: Haematologica, (2001) Vol. 86, No. 9, pp. 908-917. .
Refs: 63
ISSN: 0390-6078 CODEN: HAEMAX
COUNTRY: Italy

DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
025 Hematology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 25 Oct 2001
Last Updated on STN: 25 Oct 2001

AB Background and Objectives. Several molecular and cytogenetic advances have suggested novel therapeutic strategies that could help roach an eventual cure for multiple myeloma (MM). Evidence and Information Sources. Identification of novel, MM-specific molecular targets should pave the way for drugs that can specifically attack the neoplastic cells while sparing the normal ones. Drugs that alter the marrow microenvironment - such as bisphosphonates, proteasome inhibitors (e.g. PS-341/LDP341), lactacystin or LLNV compounds - induce apoptosis or G1 growth arrest and alter the adhesion of MM cells to marrow stroma. These drugs that modify the microenvironment have a more solid scientific basis and may, therefore, have more realistic implications in MM treatment. Of these, novel vascular endothelial growth factor (VEGF) inhibitors, such as SU5416 and SU6668, block tumor-cell adhesion and could disrupt MM cell proliferation. Similarly, tyrosine kinase inhibitors (TKI) such as fibroblast growth factor receptor (FGFR) inhibitors, may serve when the FGFR3 gene is overexpressed due to the t(4;14)(p16.3;q32) and/or is activated by point mutations. In cases carrying the translocation and expressing the IgH/WHSC1-MMSET hybrid transcripts, histone deacetylase (HDAC) inhibitors could be useful, but their possible clinical use needs to be supported by more biological studies. Tumor necrosis factor α-related apoptosis-inducing ligand (TRAIL) induces apoptosis in MM cell lines and primary cells. The proliferative signaling pathway of FGFR3 is mediated by Ras (Ras-activating mutations are frequently found in MM), which presents a possible target for farnesyltransferase inhibitors (used alone or in association with IFN-α). Perspectives. In several of these options, proclinical studies have proved encouraging, and clinical trials are now getting underway. .COPYRGT.2001, Ferrata Storti Foundation.

L38 ANSWER 27 OF 31 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2001087093 EMBASE Full-text
TITLE: Receptor tyrosine kinase inhibitors.
AUTHOR: Haluska P.; Adjei A.A.
CORPORATE SOURCE: A.A. Adjei, Division of Medical Oncology, Mayo Clinic, 200 First St SW, Rochester, MN 55905, United States. adjei.alex@mayo.edu
SOURCE: Current Opinion in Investigational Drugs, (2001) Vol. 2, No. 2, pp. 280-286. .
Refs: 72
ISSN: 0967-8298 CODEN: CIDREE
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 037 Drug Literature Index
029 Clinical Biochemistry
016 Cancer
038 Adverse Reactions Titles
030 Pharmacology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 22 Mar 2001

AB Receptor tyrosine kinases (RTKs) are a diverse group of transmembrane proteins involved in signal transduction. Their function in many cell types is to drive a wide variety of cellular functions, including growth, differentiation and angiogenesis, by transducing growth factor signals from the external milieu to intracellular processes. In malignancies, these pathways are often exploited by tumor cells to optimize tumor growth and metastasis. Indeed, alterations in RTK pathways have been implicated in oncogenic activation, tumor angiogenesis and mitogenic stimulation. Thus, RTKs are logical targets for novel anticancer agent development. There are currently a large number of small-molecule RTK antagonists in phase I to III clinical development. These agents inhibit the intracellular tyrosine kinase activity of receptors for epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF). The biology and results of clinical trials with these agents will be discussed.

L38 ANSWER 28 OF 31 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:314864 CAPLUS Full-text
DOCUMENT NUMBER: 132:344076
TITLE: Method for detecting endocrine disruptor-responsive genes and for screening endocrine disruptors
INVENTOR(S): Kondo, Akihiro; Sagawa, Hiroaki; Mineno, Junichi; Kimizuka, Fusao; Kato, Ikunoshin
PATENT ASSIGNEE(S): Takara Shuzo Co., Ltd., Japan
SOURCE: PCT Int. Appl., 81 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000026404	A1	20000511	WO 1999-JP5964	19991028
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9964878	A1	20000522	AU 1999-64878	19991028
EP 1126035	A1	20010822	EP 1999-952794	19991028
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: JP 1998-310285 A 19981030
WO 1999-JP5964 W 19991028

AB A method and compns. for detecting genes affected by endocrine-disrupting chems. and for identifying endocrine-disrupting chems. are claimed. The method comprises preparing a nucleic acid sample containing mRNAs or cDNAs originating in cells, tissues, or organisms which have been brought into contact with a sample containing the endocrine disruptor. The nucleic acid sample is hybridized with DNA arrays wherein genes which might be affected by the endocrine disruptor or DNA fragments originating in these genes have been fixed. The results obtained are then compared with the results obtained with the control sample to select the gene affected by the endocrine disruptor. Endocrine disruptors are selected from dioxins, organic chloro compds., phenols, futalic acid esters, aromatic hydrocarbons, agrochems., organic tin compds., and estrogens, among others. The effect of 3 chems., 17-β estradiol (E2), diethylstilbestrol (DES), and bisphenol A (BisA) on 33 candidate genes belonging to the categories of nuclear receptor/nuclear receptor transcriptional coupling, kinase-type signal transducer, gonad differentiation factor, oncogene, and receptor-type kinase, were examined by the method of this invention. Expression of most of the genes was either increased or decreased by exposure to these chems.

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 29 OF 31 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2001091326 EMBASE Full-text
TITLE: From oncogene to drug: Development of small molecule tyrosine kinase inhibitors as anti-tumor and anti-angiogenic agents.
AUTHOR: Morin M.J.
CORPORATE SOURCE: M.J. Morin, Pfizer Global R and D, Groton, CT 06340, United States
SOURCE: Oncogene, (27 Dec 2000) Vol. 19, No. 56, pp. 6574-6583. .
Refs: 83
ISSN: 0950-9232 CODEN: ONCNES
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English

SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 29 Mar 2001
Last Updated on STN: 29 Mar 2001

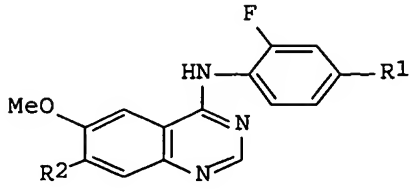
AB The confluence of two distinct but related activities in the past 10 years has dramatically accelerated efforts towards the discovery and development of novel drugs to treat cancer. The first is a rapidly emerging understanding that a number of distinct tyrosine kinases play roles in diverse but fundamentally important aspects of tumor progression (growth, survival, metastasis and angiogenesis). The second is the discovery that small molecule compounds have the capacity to potently and selectively inhibit the biochemical function of tyrosine kinases by competing for ATP binding at the enzyme catalytic site. These observations have been conjoined in major efforts to bring forward into clinical development novel cancer drugs with the potential to provide both clinical efficacy and improved tolerability. The focus of this review is on the development of small molecule tyrosine kinase inhibitors, and does not extend to other approaches that could be applied to disrupt the same pathways in clinical tumors (receptor and/or ligand competitive antibodies, intrabodies, antisense ribonucleotides, ribozymes, phosphatase inhibitors or SH2/SH3-directed agents). Selected tyrosine kinase inhibitors, known or believed to be in development in cancer treatment trials, are summarized as are some of the key issues that must be addressed if these compounds are to be developed into clinically useful cancer chemotherapeutic agents.

L38 ANSWER 30 OF 31 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2001074577 EMBASE Full-text
TITLE: Anti-angiogenic treatment strategies for malignant brain tumors.
AUTHOR: Kirsch M.; Schackert G.; Black P. McL.
CORPORATE SOURCE: M. Kirsch, Klin./Poliklin. fur Neurochirurgie, Technische Universitat Dresden, Fetscherstrasse 74, 01307 Dresden, Germany. matthias.kirsch@mailbox.tu-dresden.de
SOURCE: Journal of Neuro-Oncology, (2000) Vol. 50, No. 1-2, pp. 149-163. .
Refs: 157
ISSN: 0167-594X CODEN: JNODD2
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
008 Neurology and Neurosurgery
030 Pharmacology
005 General Pathology and Pathological Anatomy
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 8 Mar 2001
Last Updated on STN: 8 Mar 2001

AB The use of angiogenesis inhibitors may offer novel strategies in brain tumor therapy. In contrast to traditional cancer treatments that attack tumor cells directly, angiogenesis inhibitors target at the formation of tumor-feeding blood vessels that provide continuous supply of nutrients and oxygen. With respect to brain tumor therapy, inhibitors of angiogenesis display unique features that are unknown to conventional chemotherapeutic agents. The most important features are independence of the blood-brain barrier, cell type specificity, and reduced resistance. Malignant brain tumors, especially malignant gliomas, are among the most vascularized tumors known. Despite multimodal therapeutic approaches, the prognosis remains dismal. Thus, angiogenesis inhibitors may be highly effective drugs against these tumors. In a clinical setting, they could be applied in the treatment of multiple tumors or postsurgically as an adjuvant therapy to prevent recurrence. This article provides an overview of current anti-angiogenic treatment strategies with emphasis on substances already in clinical trials or candidate substances for clinical trials. The cellular and molecular basis of these substances is reviewed.

L38 ANSWER 31 OF 31 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:784580 CAPLUS Full-text
DOCUMENT NUMBER: 132:151769
TITLE: Design and Structure-Activity Relationship of a New Class of Potent VEGF Receptor Tyrosine Kinase Inhibitors
AUTHOR(S): Hennequin, Laurent F.; Thomas, Andrew P.; Johnstone, Craig; Stokes, Elaine S. E.; Ple, Patrick A.; Lohmann, Jean-Jacques M.; Ogilvie, Donald J.; Dukes, Mike;

Wedge, Steve R.; Curwen, Jon O.; Kendrew, Jane;
Lambert-van der Brempt, Christine
CORPORATE SOURCE: AstraZeneca Zeneca Pharma Centre de Recherches Z.I. La Pompelle, Reims, 51689, Fr.
SOURCE: Journal of Medicinal Chemistry (1999), 42(26), 5369-5389
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB A series of substituted 4-anilinoquinazolines and related compds. were synthesized as potential inhibitors of vascular endothelial growth factor (VEGF) receptor (Flt and KDR) tyrosine kinase activity. Enzyme screening indicated that a narrow structure-activity relationship (SAR) existed for the bicyclic ring system, with quinazolines, quinolines, and cinnolines having activity and with quinazolines and quinolines generally being preferred. Substitution of the aniline was investigated and clearly indicated that small lipophilic substituents such as halogens or Me were preferred at the C-4' position. Small substituents such as hydrogen and fluorine are preferred at the C-2' position. Introduction of a hydroxyl group at the meta position of the aniline produced the most potent inhibitors of Flt and KDR tyrosine kinases activity with IC50 values in the nanomolar range. Investigation of the quinazoline C-6 and C-7 positions indicates that a large range of substituents are tolerated at C-7, whereas variation at the C-6 is more restricted. At C-7, neutral, basic, and heteroarom. side chains led to very potent compds., as illustrated by the methoxyethoxy derivative I [R1 = 4-Cl, R2 = OCH2CH2OMe] (IC50 < 2 nM). These inhibitors proved to be very selective inhibitors of Flt and KDR tyrosine kinase activity when compared to that associated with the FGF receptor (50- to 3800-fold). Observed enzyme profiles translated well with respect to potency and selectivity for inhibition of growth factor stimulated proliferation of human umbilical vein endothelial cells (HUVECs). Oral administration of selected compds. to mice produced total plasma levels 6 h after dosing of between 3 and 49 μM. In vivo efficacy was demonstrated in a rat uterine edema assay where significant activity was achieved at 60 mg/kg with I [R1 = Me, R2 = OMe]. Inhibition of growth of human tumors in athymic mice has also been demonstrated: I [R1 = Br, R2 = 2-(1,2,3-triazol-1-yl)ethoxy] inhibited the growth of established Calu-6 lung carcinoma xenograft by 75% (P < 0.001, one tailed t-test) following daily oral administration of 100 mg/kg for 21 days.

REFERENCE COUNT: 79 THERE ARE 79 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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